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(54) Title: PHENYLOXAZOLIDINONE ANTIMICROBIALS

(57) Abstract

A compound of structural formula (I), or pharmaceutically acceptable salts thereof wherein: Q is selected from the structures i, ii, iii, iv and v. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, particularly aerobic gram-positive bacteria, including multiply-resistant staphylococci, enterococci and streptococci, as well as anaerobic organisms such as bacteroids and clostridia species, and acid-fast bacteria such as as *Mycobacterium tuberculosis* and other mycobacterial species.

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PHENYLOXAZOLIDINONE ANTIMICROBIALS

Background of the Invention

5   The subject invention discloses new and useful phenyloxazolidinone
compounds having either a pyrrolidinyl or azetidinyl moiety. The compounds are
useful antimicrobial agents, effective against a number of human and veterinary
pathogens, including gram-positive aerobic bacteria such as multiply-resistant
staphylococci, streptococci and enterococci as well as anaerobic organisms such as
10   *Bacteroides spp.* and *Clostridia spp.* species, and acid-fast organisms such as
Mycobacterium tuberculosis, Mycobacterium avium and *Mycobacterium spp.*.

Information Disclosure

The present compounds are related by their phenyloxazolidinone ring
15   structure to the compounds disclosed in the publications below except that the
subject compounds have a multi-substituted pyrrolidinyl or azetidinyl moiety. The
instant compounds are unique and have useful antibacterial activity.

PCT/US93/03570 application discloses oxazolidinones containing a substituted
diazine moiety and their uses as antimicrobials.

20   PCT/US92/08267 application discloses substituted aryl and heteroaryl-phenyl-
oxazolidinones useful as antibacterial agents.

PCT/US89/03548 application discloses 5'indolinyl-5ß-amidomethyloxazolidin-
ones, 3-(fused-ring substituted)phenyl-5ß-amidomethyloxazolidinones, and
3-(nitrogen substituted)phenyl-5ß-amidomethyloxazolidinones which are useful as
25   antibacterial agents.

Other references disclosing various oxazolidinones include US Patent
4,801,600, 4,921,869, Gregory W. A., et al., J. Med. Chem., 32, 1673-81 (1989);
Gregory W. A., et al., J. Med. Chem., 33, 2569-78 (1990); Wang C., et al.,
Tetrahedron, 45, 1323-26 (1989); and Brittelli, et al., J. Med. Chem., 35, 1156 (1992).
30   European Patent Publication 352,781 discloses phenyl and pyridyl
substituted phenyl oxazolidinones.

European Patent Publication 316,594 discloses 3-substituted styryl
oxazolidinones.

European Patent Publication 312,000 discloses phenylmethyl and
35   pyridinylmethyl substituted phenyl oxazolidinones.

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Summary of the Invention

In one aspect the subject invention is a compound of structural Formula I:

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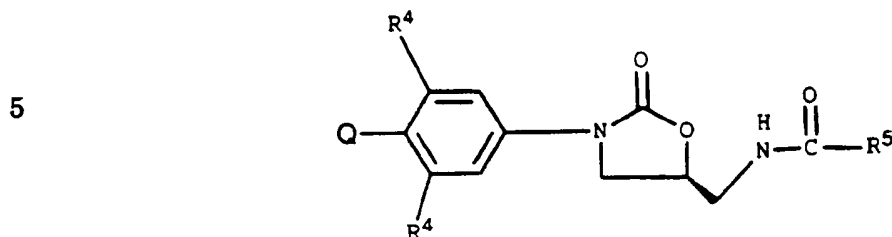
or pharmaceutically acceptable salts thereof wherein:

10   Q is selected from the structures i, ii, iii, iv and v:

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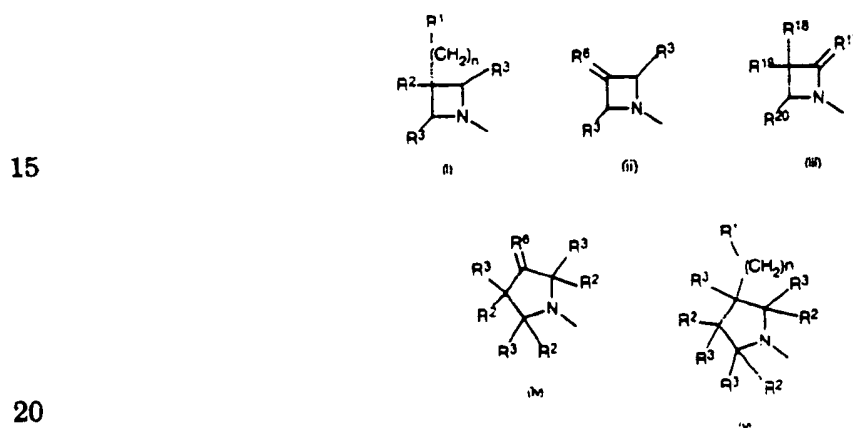
R^1 is   (a)   H or F,

25   (b) OR^7,

          (c) SR^7,

          (d) NR^8R^9,

          (e)   CN,

          (f) C_1-C_4 alkoxycarbonyl,

30   (g)   carboxamide,

          (h) C_1-C_4 acyl optionally substituted with one or more of the following:
                fluorine, hydroxy, C_1-C_4 alkoxy, C_1-C_4 acyloxy;

          (i)   NHO(C_1-C_6 alkyl) or $NHOCH_2Ph$

          (j) NSO_2R where R is C_{1-6} alkyl optionally substituted with one or more

35   F, Cl. C_{1-6} alkoxy or phenyl;

     each R^2 is independently selected from

(a)　　　H or F,

(b)　　　OH,

(c)　　　OR where R is C_1-C_6 alkyl,

(d)　　　C_1-C_4 alkyl,

5　　(e)　　　Ph;

each R^3 is independently selected from

(a)　　　H,

(b)　　　C_1-C_3 alkyl which can be optionally substituted with F, Cl, hydroxy,
C_1-C_3 alkoxycarbonyl, C_1-C_3 acyloxy, C_1-C_3 alkyoxy or $N(C_1$-C_4 alkyl$)_2$,

10　　(c)　　　phenyl,

(d)　　　pyridyl;

R^4 is independently H, OCH_3, F or Cl;

R^5 is　(a)　　　hydrogen,

(b)　　　C_1-C_8 alkyl optionally substituted with one or more of the following:

15　　　　　　　F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy,

(c)　　　C_3-C_6 cycloalkyl,

(d)　　　amino,

(e)　　　C_1-C_8 alkylamino,

(f)　　　C_1-C_8 dialkylamino,

20　　(g)　　　C_1-C_8 alkoxy;

R^6 is　(a)　　　O,

(b)　　　S,

(c)　　　NR^{10},

(d)　　　$CR^{11}R^{12}$,

25　　(e)　　　$(OR)_2$, where R = C_1-C_6 alkyl,

(f)　　　$O(CH_2)_mO$,

(g)　　　$(SR)_2$, where R = C_1-C_6 alkyl,

(h)　　　$S(CH_2)_mS$

(i)　　　to fill the valence OH and H, H and H, H and F or F and F;

30　　R^7 is　(a)　　　H,

(b)　　　C_1-C_8 alkyl optionally substituted with one or more of the following:
　　　　　　　F, Cl, -CN, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy, C_1-C_8
　　　　　　　alkoxycarbonyl, phenyl,

(c)　　　C_1-C_8 acyl optionally substituted with one or more of the following:

35　　　　　　　hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy,

(d)　　　C_1-C_8 alkoxycarbonyl,

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(e)   carboxamide, optionally substituted with a C_1-C_4 alkyl or phenyl on the carboxamide nitrogen,

(f)   phenyl, optionally substituted with one or more of the following: halogen, CN, C_1-C_3 alkoxy, C_1-C_3 alkoxycarbonyl, C_1-C_4 alkyl optionally substituted with one or more of F or C_1-C_3 alkoxy;

R^8 and R^9 are independently selected from:

(a)   H

(b) C_1-C_8 alkyl optionally substituted with one or more of the following: F, Cl, -CN, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy, C_1-C_8 alkoxycarbonyl, phenyl,

(c) C_1-C_8 acyl optionally substituted with one or more of the following: hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy, amino, C_1-C_4 acylamino, amino-C_1-C_4 acylamino,

(d)   benzoyl optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy, amino, C_1-C_4 acylamino, C_1-C_4 alkoxycarbonylamino,

(e) C_1-C_8 alkoxycarbonyl, benzyloxycarbonyl, tertbutoxycarbonyl,

(f)   carboxamide, optionally substituted with a C_1-C_4 alkyl or phenyl on the carboxamide nitrogen

(g)   trifluoracetyl

(h)   CO(C_1-C_6 alkyl) ;

R^{10} is (a)   H,

(b)   OR^7,

(c)   NHR^7,

(d) C_1-C_8 alkyl optionally substituted with phenyl;

R^{11} and R^{12} are independently selected from:

(a)   H, F,

(b) C_1-C_4 alkyl optionally substituted with halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, phenyl,

(c) C_1-C_8 acyl,

(d) C_1-C_4 alkoxycarbonyl,

(e)   CN;

R^{17} is (a)   O,

(b)   S;

R^{18} and R^{19} are independently selected from:

(a)   H.

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(b) · C$_1$-C$_4$ alkyl optionally substituted with halogen, hydroxy, C$_1$-C$_4$ alkoxy,

(c) OH,

(d) C$_1$-C$_4$ alkoxy optionally substituted with hydroxy or C$_1$-C$_4$ alkoxy,

(e) NR^{8}R^9

(f) -OC(O)C$_1$-C$_4$ alkyl;

R^{20} is (a) H,

(b) CH$_3$;

n is 0 or 1 and m is 2 or 3.

In one aspect the subject invention is a compound of structural Formula i:

In another aspect the subject invention is composed of structural Formula ii:
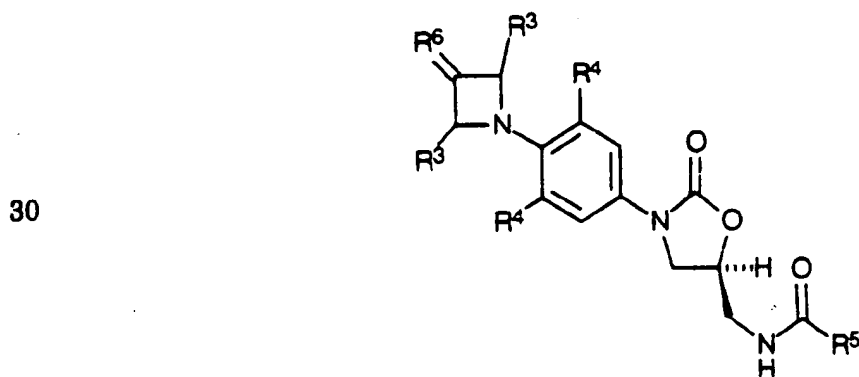
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In another aspect the subject invention is composed of structural Formula iii:

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In yet another aspect, the subject invention is a compound of structural Formula iv:

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In yet another aspect, the subject invention is a compound of structural Formula v:

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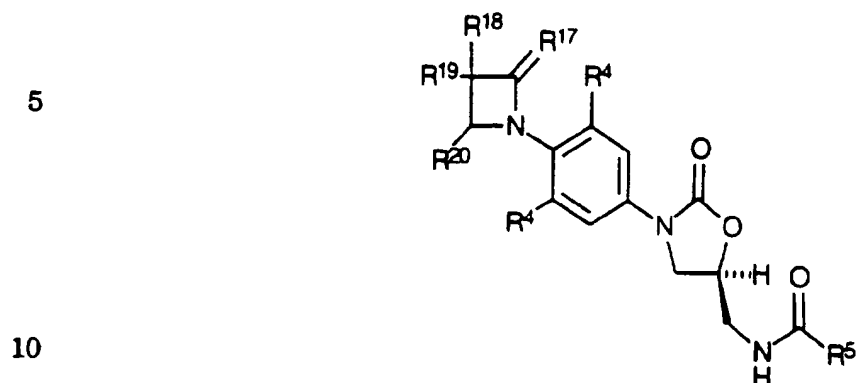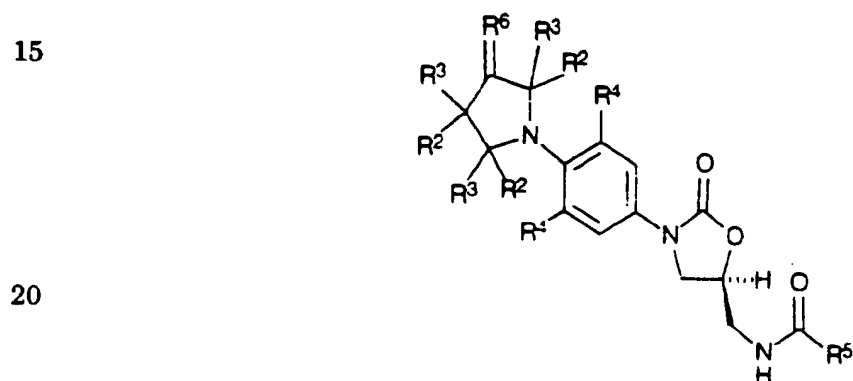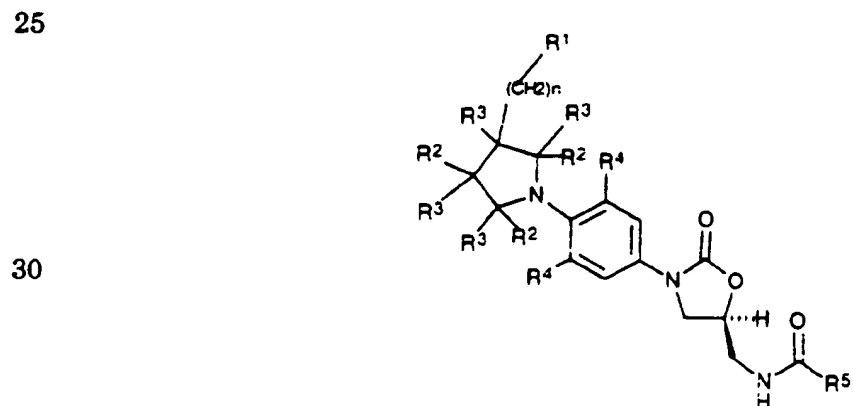
In another aspect, the subject invention is directed toward a method for treating microbial infections in humans or other warm-blooded animals by administering to a patient in need thereof an effective amount of a compound of Formula I (i-v) as described above. The compound can be administered in a

5 pharmaceutical composition either orally, parenterally or topically. Preferably the compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day, more preferably, from about 3.0 to about 50 mg/kg of body weight/day.

10 **Detailed Description of the Invention**

The present invention discloses novel substituted azetidinyl- and pyrrolidinyl-phenyloxazolidinones of structural Formula I (and as structurally represented in Formulas i-v) as described above. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, particularly aerobic

15 gram-positive bacteria, including multiply-resistant staphylococci, enterococci and streptococci, as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast bacteria such as as *Mycobacterium tuberculosis* and other mycobacterial species.

The R^4 substituents are preferably both fluorine and, more preferably,

20 fluorine and hydrogen.

The R^5 substituent is preferably hydrogen, methyl, dichloromethyl, hydroxymethyl or methoxy. More preferably R^5 is hydrogen, methoxy or methyl. It is most preferred that R^5 is methyl.

The R^6 substituent is preferably O, OCH_2CH_2O, NOH and $NOCH_3$.

25 "Alkyl" means carbon atom chains having the designated number of carbon atoms which can be either straight chained or branched.

"Alkoxy" means the designated number of carbon atoms attached to an oxygen forming such groups as methoxy ($-OCH_3$), ethyloxy, butyloxy, etc. and isomeric forms thereof.

30 "Acyloxy" means the designated number of carbon atoms to form an organic acid where the OH group has been deleted, such as acetyl, $CH_3 CO$-; benzoyl, $C_6 H_5CO$-.

Cycloalkyl" means the designated number of carbon atoms forming cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. and isomeric forms thereof.

35 "Ph" means phenyl. "Carbonyl" is a -C(=O)- moiety. "Amino" means an NH_2, "alkylamino" is where one of the hydrogen positions is replaced by an alkyl

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and "dialkylamino" is where both hydrogens are replaced by an alkyl group.

"Pharmaceutically acceptable salts" are acid addition salts which can be prepared by any of the art recognized means. Typical, acid addition salts include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate,

5   lactate, malate, succinate, tartrate, cyclohexanesulfamates, methanesulfonates, ethanesulfonates, benxenesulfonates, toluenesulfonates, fumarates and other pharmaceutically acceptable couter ions for amines.

Azetindinyl-Phenyloxazolidinones:

The preferred absolute configuration at C-5 of the oxazolidinone ring of

10   compounds claimed in this invention is as represented in the structures of Formula i and ii. This absolute configuration is called (S) under the Cahn-Ingold-Prelog nomenclature system. It is this (S)-enantiomer which is pharmacologically active as an antibacterial. The racemic mixture is useful in the same way and for the same purpose as the pure (S)-enantiomer; the difference is that twice as much racemic

15   material must be used to produce the same antibacterial effect. It will be apparent to one skilled in the art that when a chiral center (R not H) is present in the azetidine fragment of compounds of structural Formula i, ii and iii, then diastereomers are possible. These diastereomers, in racemic and enantiomerically enriched forms, are also within the scope of the compounds of Formula i, ii and iii of

20   the invention.

The preferred method of preparation of oxazolidinones of Formula i, ii and iii in enantiomerically pure form is depicted in Charts I-VI. Charts I-VI contain generic structural representations for the preparation of the various compounds of the invention centered around the core cyclic structure wherein Q is i, ii or iii.

25   As shown in Chart I, 3-hydroxyazetidines of structure 1 can be deprotonated with a suitable base, for example sodium hydride, in a suitable solvent, for example tetrahydrofuran (THF), and then alkylated with alkyl halides, for example methyl iodide, to give the azetidine ethers 2 (R^{13} = alkyl). If desired, aryl azetidine ethers 2 (R^{13} = optionally substituted phenyl) can be prepared from azetidinol 1 by

30   employing known procedures (Taylor, C. R., Jr.; Cale, A. D., Jr.; Stauffer, H. F., Jr. U.S. Patent 4 956 359, 1990). The benzhydryl group of 1 and 2 is removed by hydrogenolysis in the presence of a mineral acid, for example hydrochloric acid, and in the presence of a suitable catalyst, for example palladium hydroxide on carbon, in a suitable solvent, such as methanol, to give the azetidines 3 (R^{13} = H, alkyl,

35   phenyl. Compounds of structure 3 are then reacted with a functionalized nitrobenzene 4 (X = halogen or trifluoromethanesulfonate) in the presence of a

suitable base/solvent combination, for example dibasic potassium phosphate in dimethyl sulfoxide or N,N-diisopropylethylamine in acetonitrile or THF, and at a suitable temperature, typically ambient temperature to 70°C, to afford the adduct 5. If it is desired that R^1 of a compound of structural Formula i or an advanced

5   intermediate be hydroxy, then a suitable protecting group, such as the *tert*-butyldimethylsilyl moiety, is appended by reacting 5 (R^{13} = H) with *tert*-butyldimethylsilyl chloride in the presence of imidazole in a suitable solvent such as N,N-dimethylformamide (DMF) at ambient temperature to give 5 (R^{13} = *tert*-butyldimethylsilyl). It will be apparent to those skilled in the art that this

10   protecting group is merely representative and that alternative protecting groups, such as those described in Greene, T. W.; Wuts, P. G. M. "Protective Groups in Organic Synthesis", 2nd ed.; John Wiley & Sons: New York, 1991, can be employed. The nitro group of 5 is then reduced by catalytic hydrogenation in the presence of a suitable catalyst, such as 10% palladium/carbon or W-2 Raney nickel, and in an

15   appropriate solvent, for example THF/H$_2$O. When this latter solvent system is utilized, the reaction mixture is first filtered to remove the catalyst and the filtrate containing the intermediate aniline is then treated with, for example, sodium bicarbonate and benzyl or methyl chloroformate to give the corresponding benzyl (R^{14} = CH$_2$Ph) or methyl (R^{14} = CH$_3$) urethane derivatives 6. The urethanes 6 are

20   then deprotonated with a suitable base such as n-butyllithium (n-BuLi), lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide, in a suitable solvent such as tetrahydrofuran (THF) and at a suitable temperature such as -78 to -40°C to give a lithiated intermediate which is then treated with commercially available (-)-(R)-glycidyl butyrate. Warming to ambient temperature then directly affords the

25   5-(hydroxymethyl)oxazolidinones 7 in enantiomerically enriched form.
        As shown in Chart II, compound 7 is then converted to the corresponding mesylate 8 (R^{15} = methyl) or aryl sulfonate 8 (R^{15} = ArSO$_2$, for example *p*-toluenesulfonyl) by the action of, for example, methanesulfonyl chloride/pyridine or methanesulfonyl chloride/triethylamine/dichloromethane or *p*-toluenesufonyl

30   chloride/pyridine. The resultant sulfonate derivative 8 is then reacted with an azide sourc such as sodium or potassium azide in an aprotic solvent such as N,N-dimethylformamide (DMF) or 1-methyl-2-pyrrolidinone optionally in the presence of a catalyst such as 18-crown-6 at a temperature of 50-90 °C to afford the azide 9. The azide is then reduced by hydrogenation with palladium on carbon or a platinum

35   catalyst in an appropriate solvent such as ethyl acetate or methanol to give the corresponding amine 10. Alternatively, the azide 9 can be reduced by treatment

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with a trivalent phosphorus compound such as triphenylphosphine in a suitable
solvent such as tetrahydrofuran followed by the addition of water. The intermediate
amine **10** may also be prepared by treatment of the phthalimide derivative **11**
(obtained by reacting sulfonate **8** with potassium phthalimide in a suitable solvent,
5   for example, acetonitrile at reflux temperature) with methylamine in ethanol/H_2O at
reflux temperature. Alternatively, the amine **10** may be prepared directly from the
mesylate **8** by ammonolysis with aqueous ammonium hydroxide in a solvent system
consisting of H_2O/ispropanol/THF in a sealed reaction vessel immersed in a 70-95 °C
oil bath. The amine **10** is then acylated by reactions known to those skilled in the
10   art to give oxazolidinones of structure **12**. For example, the amine can be reacted
with an acid chloride or anhydride in a basic solvent such as pyridine at a
temperature ranging from -30 to 30 °C to provide the acylated compound **12** (R^5 =
optionally substituted alkyl). It will be apparent to one skilled in the art that other
carbonyl groups within the scope of this invention can be readily appended to the
15   amine **10** by standard acylation techniques, for example those highlighted in March,
J. "Advanced Organic Chemistry", 3rd ed.; John Wiley & Sons: New York, 1985; p
370-375, to give additional examples of **12**. If it is desired that R^{13} be H, then the
appended *tert*-butyldimethylsilyl protecting group of selected examples of **12** is
removed employing appropriate conditions, such as those noted in Greene, T. W.;
20   Wuts, P. G. M. "Protective Groups in Organic Synthesis", 2nd ed.; John Wiley &
Sons: New York, 1991, especially aqueous hydrofluoric acid in acetonitrile at
ambient temperature, to give the corresponding alcohol. The compounds of structure
12 (R^{13} = H, alkyl, optionally substituted phenyl) represent examples of azetidine-
substituted oxazolidinone antibacterial agents of Formula I, which are the subject of
25   this invention.

The azetidine-containing oxazolidinones **12**, themselves examples of
antibacterial agents of structural Formula i, can be further elaborated to additional
compounds of Formula i and also examples of structural Formula ii as shown in
Chart III. For example, **12** (R^{13} = H) can be oxidized to the corresponding
30   azetidinone **13** by reacting it with catalytic tetra-*n*-propylammonium perruthenate in
the presence of *N*-methylmorpholine *N*-oxide and molecular sieves in
acetonitrile/dichloromethane. Compound **13** is an example of an antibacterial agent
of structural Formula ii. The ketone moiety of **13** is amenable to further
modification. Reaction of **13** with Lawesson's reagent or alternative reagents, as
35   described in March, J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons:
New York, 1992; p 893-894, provides the corresponding thioketone **14** (R^6 = S).

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Oximes 14 (for example, R^6 = NOH and NOCH$_3$) are readily prepared by reacting 13 with, for example, hydroxylamine hydrochloride or methoxylamine hydrochloride in the presence of a suitable base, such as pyridine, and in an appropriate solvent, for instance methanol, at ambient temperature. Various hydrazone derivatives (R^6

5   = NNHR^7) can be prepared by reacting 13 with hydrazines, as described in Greene, T. W.; Wuts, P. G. M. "Protective Groups in Organic Synthesis", 2nd ed.; John Wiley & Sons: New York, 1991, p 212-213 and March, J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons: New York, 1992; p 904-905. Imines 14 (R^6 = N-alkyl or N-aryl) are synthesized by treating 13 with primary amines, as described in March,

10   J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons: New York, 1992; p 896-897. Olefinic derivatives (14: R^6 = CR^{11}R^{12}) are prepared by reacting 13 with various olefinating reagents, such as phosphorus ylides and the like, which are known to one skilled in the art. Representative examples are described in March, J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons: New York, 1992; p 956-

15   963. For the case where R^6 is CF$_2$ this would involve treatment of ketone 13 with (NaO$_2$CCF$_2$Cl) sodium difluorochloroacetate and triphenylphosphate, as described in Tetrahedron Letters 1964, p 1461. The resulting olefinic bond can be reduced by catalytic hydrogenation or other methods known to one skilled in the art to furnish examples of structural Formula i. Other compounds of structure 14, for example

20   cyclic and acyclic ketals and dithio ketals, can be prepared by reacting compound 13 with diols, dithiols, alcohols or thiols under conditions, for example, described in Greene, T. W.; Wuts, P. G. M. "Protective Groups in Organic Synthesis", 2nd ed.; John Wiley & Sons: New York, 1991, p 177-207. Compound 12 (R^{13} = H) can also be converted to various derivatives 15 (R^{16} = optionally substituted acyl,

25   alkoxycarbonyl, carboxamide, etc.) by treatment of 12 with various carbonyl derivatives, such as anhydrides, alkyl chloroformates, isocyanates and the like, in the presence of appropriate bases, and in suitable solvents known to one skilled in the art. Compounds 14 and 15 represent examples of oxazolidinone antibacterial agents of structural Formula i and ii.

30   Charts IV-VI outline procedures to prepare examples of structural Formula i wherein R^1 is a group other than OR^7. As shown in Chart IV, the mesylate 16, obtained by reacting azetidinol starting material 1 with methanesulfonyl chloride in the pres nce of triethylamine and dichloromethane, is reacted with a variety of nucleophiles. For example, treatment of 16 with ammonia, primary amines or

35   secondary amines affords 3-aminoazetidines of structure 17. Similarly, treatment of 16 with thiolates or cyanide provides the adducts 18 and 19, respectively.

Compound 19 can be reduced with lithium aluminum hydride and the like to the corresponding 3-(aminomethyl)azetidine 20. Compound 19 can also be converted to the carboxylate derivative 21. Those skilled in the art can further transform the carboxylate moiety of 21 to the corresponding carboxamide or various acyl groups

5   which, after further elaboration, comprise additional examples of antibacterial agents of structural Formula i. Compounds 17 and 20 can be further N-alkylated by procedures known to one skilled in the art, including treatment of 17 and 20 with alkyl halides or tosylates in the presence of a suitable base. Alternatively, selected alkyl groups can be appended on the nitrogen of 17 and 20 by a reductive alkylation

10 procedure as described in March, J. "Advanced Organic Chemistry", 4th ed.; John Wiley & Sons: New York, 1992; p 898-900. In the cases of amino intermediates 17 and 20, when a free NH is present, it is necessary to protect these moieties to enable some subsequent reactions to proceed uneventfully. The amino group can be converted to the corresponding t-butyl carbamate (BOC), benzyl carbamate (Cbz),

15 trifluoroacetamide, or phthalimide derivatives and the like, as required, employing procedures described in Greene, T. W.; Wuts, P. G. M. "Protective Groups in Organic Synthesis", 2nd ed.; John Wiley & Sons: New York, 1991, p 309-403. The benzhydryl protecting group of 17-21 is then removed by hydrogenolysis in the presence of a suitable catalyst, for example palladium hydroxide on carbon, and in

20 the presence of a mineral acid, for example hydrochloric acid, to give the intermediate azetidines 22 (R^1 not OR^7).

Chart V outlines the elaboration of intermediate azetidines 22 to examples of structural Formula i (R^1 not OR^7). The chemistry is essentially identical to that described in Chart I. Compound 22 is initially converted to the nitrobenzene

25 derivative 23. Reduction and conversion to carbamates of structure 24 is accomplished as described previously. As described in Chart I, intermediate 24 is elaborated to the optically active 5-(hydroxymethyl)oxazolidinone 25. Application of procedures outlined in Chart II then allows for conversion of 25 to compounds of structure 26. Removal of any appended protecting groups, for example BOC groups

30 on compounds where R^1 is amino, is achieved by methods known to one skilled in the art, for instance those described in Greene, T. W.; Wuts, P. G. M. "Protective Groups in Organic Synthesis", 2nd ed.; John Wiley & Sons: New York, 1991. The resultant free amino group can then be N-alkylated or N-acylated, if desired. to give additional compounds of structure 26. which are examples of oxazolidinone

35 antibacterial agents of structural Formula i.

Chart VI depicts a variation of the chemistry outlined in Chart IV wherein

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the hydroxyazetidinylphenyloxazolidinone intermediate 12 (R^{13} = OH) is converted to the corresponding mesylate 27 by the action of methanesulfonyl chloride in the presence of a suitable base, such as triethylamine, and in an appropriate solvent, for example dichloromethane. The same nucleophilic displacements described in Chart

5   IV for the mesylate 16 can be carried out on the more functionalized mesylate 27 to give compounds 28-30. Employing procedures similar to those described in Chart IV, 30 can be converted to the compounds 31 and 32. Compounds 28-32 are examples of oxazolidinone antibacterial agents of structural Formula i, which are the subject of this invention. It will be apparent to one skilled in the art that

10   compounds 28-32 are merely representative examples and are themselves amenable to further chemical modification to give additional examples of structural Formula i.

Chart VII outlines procedures to prepare compounds of structural Formula iii. 2-Azetidinones of structure 33 are treated with an appropriate base, for example sodium hydride, in a suitable solvent, for instance THF, to give a deprotonated

15   intermediate which is then reacted with a functionalized nitrobenzene derivative 4 (X = halogen) to furnish the adduct 34. It will be apparent to one skilled in the art that appropriate protecting groups, for example those described in Greene, T. W.; Wuts, P. G. M. "Protective Groups in Organic Synthesis", 2nd ed.; John Wiley & Sons: New York, 1991, are required for selected R^{18} and R^{19} substituents of

20   compound 33. Intermediate 34 can be converted via steps outlined in Charts I and II to compounds of structure 35, themselves examples of structural Formula iii, which are the subject of this invention. Alternatively, the azetidinyl-substituted intermediate 36, prepared via procedures outlined in Charts I and II, is oxidized to the corresponding azetidinone 35 (R^{17} = O) with, for example, catalytic ruthenium

25   tetroxide in the presence of a suitable oxidant, such as sodium metaperiodate, and in a suitable solvent sytem, for example ethyl acetate/water. To prepare examples of compound 35 where R^{17} is S, selected azetidinone intermediates are reacted with Lawesson's reagent or the like.

Examples of azetindinyl-phenyloxazolidinones that can be prepared as part of

30   this invention are as follows:

1.   (S)-N-[[3-[3-fluoro-4-(3-methoxy-1-azetidinyl)phenyl]-2-oxo-5-oxazolidinyl]m thyl]acetamide

2.   (S)-N-[[3-[3-fluoro-4-(3-hydroxy-1-azetidinyl)phenyl]-2-oxo-5-

35   oxazolidinyl]methyl]acetamide

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3.   (S)-N-[[3-[3-fluoro-4-[3-[N-(2-fluoroethyl)-N-methylamino]-1-
      azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

4.   (S)-N-[[3-[3-fluoro-4-(3-oxo-1-azetidinyl)phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

5.   (S)-N-[[3-[3-fluoro-4-[3-(methoxyimino)-1-azetidinyl]phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

6.   (S)-N-[[3-[3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

7.   (S)-N-[[3-[3-fluoro-4-(3-hydroxy-3-methyl-1-azetidinyl)phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

8.   (S)-N-[[3-[3-fluoro-4-(2-oxo-1-azetidinyl)phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

9.   (S)-N-[[3-[3-fluoro-4-(3-hydroxy-2-oxo-1-azetidinyl)phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

10.   (S)-N-[[3-[3-fluoro-4-(3-methoxy-2-oxo-1-azetidinyl)phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

11.   N-[[3-[3-fluoro-4-(3-methyl-2-oxo-1-azetidinyl)phenyl]-2-oxo-(5S)-
      oxazolidinyl]methyl]acetamide

12.   (S)-N-[[3-[3-fluoro-4-(3,3-dimethyl-2-oxo-1-azetidinyl)phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

13.   (S)-N-[[3-[3-fluoro-4-[3-(hydroxyimino)-1-azetidinyl]phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

14.   N-[[3-[3-fluoro-4-[(2R)-methyl-3-oxo-1-azetidinyl]phenyl]-2-oxo-(5S)-
      oxazolidinyl]methyl]acetamide

15.   N-[[3-[3-fluoro-4-[(2S)-methyl-3-oxo-1-azetidinyl]phenyl]-2-oxo-(5S)-
oxazolidinyl]methyl]acetamide

16.   N-[[3-[3-fluoro-4-[3-(methoxyimino)-(2R)-methyl-1-azetidinyl]phenyl]-2-oxo-
(5S)-oxazolidinyl]methyl]acetamide

17.   N-[[3-[3-fluoro-4-[3-(methoxyimino)-(2S)-methyl-1-azetidinyl]phenyl]-2-oxo-
(5S)-oxazolidinyl]methyl]acetamide

18.   (S)-N-[[3-[3-fluoro-4-[3-(difluoromethylene)-1-azetidinyl]phenyl]-2-oxo-5-
oxazolidinyl]methyl]acetamide

19.   (S)-N-[[3-[3-fluoro-4-[3-(methoxymethylene)-1-azetidinyl]phenyl]-2-oxo-5-
oxazolidinyl]methyl]acetamide

20.   (S)-N-[[3-[3-fluoro-4-[3-(hydroxyacetyl)-1-azetidinyl]phenyl]-2-oxo-5-
oxazolidinyl]methyl]acetamide

21.   (S)-N-[[3-[3-fluoro-4-[3-(methoxyamino)-1-azetidinyl]phenyl]-2-oxo-5-
oxazolidinyl]methyl]acetamide

22.   N-[[3-[3-fluoro-4-[2,4-dimethyl-3-oxo-1-azetidinyl]phenyl]-2-oxo-(5S)-
oxazolidinyl]methyl]acetamide

23.   N-[[3-[3-fluoro-4-[2,4-dimethyl-3-(methoxyimino)-1-azetidinyl]phenyl]-2-oxo-
(5S)-oxazolidinyl]methyl]acetamide

24.   N-[[3-[3-fluoro-4-[2,4-dimethyl-3-methoxy-1-azetidinyl]phenyl]-2-oxo-(5S)-
oxazolidinyl]methyl]acetamide

25.   (S)-N-[[3-[3-fluoro-4-[(3S)-methoxy-(2R)-methyl-1-azetidinyl]phenyl]-2-oxo-5-
oxazolidinyl]methyl]acetamide

26.   (S)-N-[[3-[3-fluoro-4-[(3R)-methoxy-(2S)-methyl-1-azetidinyl]phenyl]-2-oxo-5-
oxazolidinyl]methyl]acetamide

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27.   (S)-N-[[3-[3-fluoro-4-[(3S)-hydroxy-(2R)-methyl-1-azetidinyl]phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

28.   (S)-N-[[3-[3-fluoro-4-[(3R)-hydroxy-(2S)-methyl-1-azetidinyl]phenyl]-2-oxo-5-
5   oxazolidinyl]methyl]acetamide

29.   (S)-N-[[3-[3-fluoro-4-(3-fluoro-1-azetidinyl)phenyl]-2-oxo-5-oxazolidinyl]-
      methyl]acetamide

10   30.   (S)-N-[[3-[3-fluoro-4-[3-fluoro-(2R)-methyl-1-azetidinyl]phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

31.   (S)-N-[[3-[3-fluoro-4-[3-fluoro-(2S)-methyl-1-azetidinyl]phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

15

32.   (S)-N-[[3-[3-fluoro-4-[3-[(hydroxyacetyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

33.   (S)-N-[[3-[3-fluoro-4-[3-[(methanesulfonyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-
20   oxazolidinyl]methyl]acetamide

34.   (S)-N-[[3-[3-fluoro-4-[3-[(formyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

·25   35.   (S)-N-[[3-[3-fluoro-4-[3-[(acetyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

36.   (S)-N-[[3-[3-fluoro-4-[3-[(methoxycarbonyl)amino]-1-azetidinyl]phenyl]-2-oxo-5-
      oxazolidinyl]methyl]acetamide

30

37.   (S)-N-[[3-[3-fluoro-4-[3-[(benzyloxycarbonyl)amino]-1-azetidinyl]phenyl]-2-oxo-
      5-oxazolidinyl]methyl]acetamide

Pyrrolidinyl-Phenyloxazolidinones:

The present invention discloses novel substituted pyrrolidinyl phenyloxazolidinones
35   according to the structural Formulas iv and v, above. The compounds are useful
      antimicrobial agents, effective against a number of human and veterinary pathogens

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particularly aerobic Gram-positive bacteria, including multiply-antbiotic resistant staphylococci and streptococci, as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as *Mycobacterium tuberculosis* and other mycobacterium species.

5   The most preferred compounds in this series would be prepared as the optically pure enantiomers having the (S)- configuration according to the Cahn-Ingold-Prelog notation at C5 of the oxazolidinone ring. Optically pure material could be prepared by one of a number of asymmetric syntheses or by resolution from a racemic modification by selective crystallization of a salt from, for example, the

10   racemic modification of intermediate amine 11 (as described in Chart XII) with an appropriate optically active acid such as dibenzoyl tartarate or 10-camphorsulfonic acid, followed by treatment with base to afford the optically active amine. Although the (S)- enantiomer of this series of compounds is preferred since it is pharmacologically active as an antibacterial, the racemic modification is also useful

15   in the same manner as the pure (S)- enantiomer; the difference being that twice as much racemic material is required to elicit the same antibacterial effect. In addition, it will be apparent to one skilled in the art that when a chiral center is present on the pyrrolidine moiety of compounds of structural Formula iv and v that diastereoisomers are possible. These diastereomers, either in the racemic or

20   configurationally enriched forms, are also within the scope of the compounds of Formulas iv and v of this invention.

          The preferred method of preparation for the pyrrolidinyl phenyloxazolidinones of Formula iv and v in enantiomerically pure form is depicted in Charts XI-XIX. Charts XI - XIX contain generic structural representations for the

25   preparation of the various compounds of the invention centered around the core cyclic structure wherein Q is iv or v.

          As shown in Chart XI, derivatives of structure 1, either commercially available or prepared by modification of literature methods, (US 4,753,953) can be protected with a diol, such as ethylene glycol, under conditions of acid catalysis with

30   azeotropic removal of water to form the acetal 2. The N-benzyl group of 2 is then removed by hydrogenolysis in the presence of a noble metal catalyst, such as palladium on carbon or palladium hydroxide on carbon, in a suitable solvent, to give the pyrrolidine derivative 3. Pyrrolidine derivative 3 can be treated with a nitrobenzen derivative 4 (Y = halogen or trifluoromethanesulfonate) in a suitable

35   base and solvent combination, for example dibasic potassium phosphate in DMSO, and a suitable temperature, typically ambient to 90°C, to afford adduct 5. The nitro

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group of 5 is then reduced by catalytic hydrogenation in the presence of catalysts such as palladium on carbon or W-2 Raney nickel in a suitable solvent, such as ethyl acetate or tetrahydrofuran (THF) to give the aniline derivative 6. When THF is used as the solvent for this reduction, it is not necessary to remove the catalyst by
5   filtration or isolate aniline derivative 6 but merely to purge the reaction vessel with an inert gas such as nitrogen add saturated aqueous sodium bicarbonate solution and treat the resulting cooled mixture with either benzyl or methyl chloroformate to give the corresponding benzyl (R^{14} = CH_2Ph) or methyl carbamate (R^{14} = CH_3) derivatives 7. Either of the carbamate derivatives 7 can be deprotonated with a
10   lithium base such as n-butyllithium, lithium diisopropyl amide (LDA), or lithium bis(trimethylsilyl)amide (LHMDS), in a suitable solvent, such as THF, N, N-dimethylformamide (DMF), or mixtures thereof, at a suitable temperature, such as -78°C to -40°C to give a lithiated intermediate which is directly treated with commercially available (R)-(-)-glycidyl butyrate. Warming this reaction mixture to
15   ambient temperature then affords the (hydroxymethyl)oxazolidinones 8 in highly enantiomerically enriched form.
         As shown in Chart XII, compound 8 can be converted to the corresponding mesylate (R^{15} = CH_3) or tosylate (R^{15} = p-$CH_3C_6H_4$) by treatment with methanesulfonyl chloride in the presence of triethylamine or pyridine or p-
20   toluenesulfonyl chloride in the presence of pyridine. The resulting sulfonate derivative 9 can then be treated with an alkalai metal azide such as sodium or potassium azide in an aprotic dipolar solvent such as DMF or N-methylpyrrolidinone (NMP) with an optional catalyst such as 18-crown-6 at a temperature in the range of 50-90°C to afford azide 10. The azide 10 can be reduced to the corresponding amine
25   11 by hydrogenation in the presence of a palladium, platinum or nickel catalyst, in an appropriate solvent such as ethyl acetate, THF, or methanol. Alternatively, azide 10 can be reduced by treatment with triphenylphoshine or other trivalent phosphorus compounds in a solvent such as THF, followed by addition of water. Amine 11 can also be prepared by treatment of sulfonate 9 with potassium
30   phthalimidate in DMF at 40-90°C or in refluxing acetonitrile to afford the phthalimide 12 which is then deprotected by treatment, for example, with aqueous methylamine in refluxing ethanol affording 11. A more direct route to amine 11 is the treatm nt of sulfonate 9 with aqueous ammonia solution in an isopropyl alcohol-THF s lvent system in a sealed tube heated at 75-105°C in an oil bath. Amine 11 is
35   then acylated by reactions well-known to those skilled in the art to give (acylaminomethyl)oxazolidinones of structure 13. For example, amine 11 can be

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treated with an acid chloride or anhydride in the presence of a base such as pyridin or triethylamin at temperatures ranging from -40-40°C to provide the acyl derivative 13 (R^5 = optionally substituted alkyl). It can be seen that under similar reaction conditions that other acyl derivatives, such as carbamates, can be readily

5   prepared. Finally, treatment of 13 with aqueous acid, such as p-toluenesulfonic acid in aqueous acetone, will hydrolyze the acetal functionality to afford the corresponding carbonyl derivative 14 which represents an example of pyrrolidinone-substituted antibacterial agents of Formula iv. It can be seen by those skilled in the art that other embodiments of a compound of Formula iv can be prepared from 14.

10   Reaction of 14 with Lawesson's reagent or other alternative reagents such as hydrogen sulfide would afford the thioketone derivative 15 (R^6 = S). Oximes (R^6 = NHOH or $NHOCH_3$) can be prepared from 14 by treatment with either hydroxylamine hydrochloride or methoxyamine hydrochloride in the presence of a base such as pyridine or sodium acetate in a solvent such as methanol. Hydrazone

15   derivatives (R^6 = $NNHR^{12}$) can be prepared by treatment of 14 with hydrazine derivatives. Similarly, imines (R^6 = NR^{12}) can be prepared by treatment of 14 with a primary amine. Olefinic derivatives (R^6 = $CR^{11}R^{12}$) can be prepared by treatment of 14 with various olefination reagents such as phosphorus ylides (Wittig reagents), phosphonate esters (Horner-Emmons Reagents) or other reagents known to those

20   skilled in the art. It can easily be seen that reduction of the olefinic bond by catalytic hydrogenation or other methods will provide examples of structural Formula v.

Charts XIII-XV outline the preparation of examples of structural Formula v wherein R^1 = OR^7, R^3 = H and n = 0. As shown in Chart XIII, intermediate 1,

25   described in Chart XI is reduced to the alcohol 16 by treatment with any of a number of standard hydride reducing agents such as sodium borohydride, lithium aluminum hydride or the like. The benzyl protecting group of 16 can then be subsequently removed by hydrogenolysis using a catalyst such as palladium hydroxide on carbon, or 10% palladium on carbon to give amino alcohol 17. It must

30   be noted here that some examples of 17 may be commercially available, but the possibility of the *de novo* synthesis of 17 must be considered, in order to include more complex exampl s of high antibacterial interest. Amino alcohol 17 can then be allowed to react with a nitrobenzene derivative such as 4 (Y = halogen or trifluoromethanesulfonate), in the presence of an appropriate base such as dibasic

35   potassium phosphate in a suitable solvent, such as dimethylsulfoxide at temperatures in the range of 40-90°C to afford 18. It will be apparent to those

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skill d in the art that subsequent transformations of 18 will require that the
hydroxyl group be protected. This can be accomplished, for example, by preparation
of the *tert*-butyldimethyl silyl ether 19 (R = Si(CH$_3$)$_2$*t*-Bu) by treatment of 18 with
tert-butyldimethylchlorosilane in the presence of a base such as imidazole or
5   diisopropylethyl amine, optionally in the presence of 4-dimethylaminopyridine as a
catalyst, in a suitable solvent such as DMF, THF, or dichloromethane. The nitro
group of 19 can be reduced by hydrogenation in the presence of a catalyst such as
10% palladium on carbon or W-2 Raney nickel in a solvent such as THF or ethyl
acetate to give aniline derivative 20. Aniline derivative 20 is not routinely isolated
10   but is directly treated with saturated sodium bicarbonate and an alkyl chloroformate
derivative such as benzyl chloroformate or methyl chloroformate to give the
corresponding benzyl (R^{14} = CH$_2$Ph) or methyl (R^{14} = CH$_3$) carbamate derivative
21. Carbamate derivative 21 can then be deprotonated by a base such as n-
butyllithium or lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide
15   (LHMDS) in a solvent such as THF or DMF or mixtures thereof, at a temperature in
the range -78°C to -40°C to give a lithiated derivative which is treated with the
commercially available (R)-(-)-glycidyl butyrate. The resulting mixture is then
warmed to ambient temperature to directly afford the
(hydroxymethyl)oxazolidinones 22.

20   It can be seen by those skilled in the art that intermediate oxazolidinone 22
can be used in a number of ways to prepare various embodiments of compounds of
structural Formula iv. As Shown in Chart XIV, oxazolidinone 22 can be converted
to (acylaminomethyl)oxazolidinone 23 by a sequence of reactions identical with that
used to convert compound 8 to compound 13 in Chart XII. The protecting group of
25   23 (R = Si(CH$_3$)$_2$t-Bu) can be removed by standard methods known to those skilled
in the art, such as treatment with tetrabutylammonium fluoride in THF to afford
alcohol 24, which is an example of a compound of structural Formula v. Compound
24 can be converted to a number of derivatives 23 (R = R^7 = optionally substituted
acyl, alkoxycarbonyl, carboxamide, etc.) by treatment with various carbonyl
30   derivatives, such as anhydrides, acyl chlorides, alkyl and aryl chloroformates,
isocyanates, and the like, using appropriate bases and catalysts in suitable solvents
known to one skilled in the art. Thus, compounds 23 and 24 represent examples of
oxazolidinone antibacterial agents of structural Formula v.

         Another use of intermediate oxazolidinone 22 is illustrated in Chart XV. As
35   shown. 22 (R = Si(CH$_3$)$_2$t-Bu) can be protected, for example, by treatment with *tert*-
butydiphenylchlorosilane and an appropriate base such as diisopropylethylamine

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and a catalyst such as 4-dimethylaminopyridine in a suitable solvent, such as dichloromethane, THF, or the like to give *bis*-protected derivative 25 (R = Si(CH$_3$)$_2$t-Bu, R^1 = SiPh$_2$t-Bu). *Bis*-protected derivative 25 is selectively deprotected to remove the *tert*-butyldimethylsilyl ether protecting group by treatment with acetic

5   acid using a co-solvent of water and THF in a variety of proportions at temperatures in the range 50-100°C to afford alcohol 26. Alcohol 26 can be alkylated on the unprotected hydroxyl group by treatment with a suitable base, such as sodium hydride, in a dipolar aprotic solvent such as THF, DMF or the like, in the presence of an alkyl halide such as methyl iodide or its substituted derivatives to give silyl

10   ether 25 (R = R^7 = straight or branched chain alkyl, R^1 = SiPh$_2$t-Bu). The silicon protecting group of 25 can then be removed by treatment with tetrabutylammonium fluoride in a solvent such as THF to afford alcohol 27 (R = straight or branched chain alkyl). Alcohol 27 can then be converted to (acylaminomethyl)oxazolidinone derivative 28 (R^7 = straight or branched chain alkyl) by a sequence of reactions

15   identical with that used to convert 8 to 13 in Chart XII. (Acylaminomethyl) oxazoldinone derivative 27 is an example of an oxazoldinone antibacterial agent of strucural Formula v.

        Charts XVI-XIX outline the preparation of examples of structural Formula v where R^1 is the substituted amino moiety. Chart XVI oulines the case where R^1 =

20   NHR and n = 0. As shown, aminopyrrolidine 29, either available commercially or prepared by methods well known in the art optionally protected as either the trifluoroacetamide (R = COCF$_3$) or the *tert*-butoxycarbonyl derivative (R = CO$_2$t-Bu) is hydrogenolyzed in the presence of a suitable catalyst such as palladium hydroxide on carbon in an appropriate solvent such as methanol to remove the benzyl

25   protecting group affording pyrrolidine 30. Pyrrolidine 30 can be reacted with a nitroaromatic compound such as 4 in the presence of a suitable base, such as dibasic potassium phosphate, in an appropriate solvent, such as dimethyl sulfoxide (DMSO) or DMF to afford displacement product 31. The nitro group of 31 is reduced by hydrogenation in the presence of 10% palladium on carbon or W-2 Raney nickel in a

30   suitable solvent such as THF or ethyl acetate to afford aniline derivative 32. The aniline derivative 32 is not routinely isolated, but generally is treated directly with saturated sodium bicarbonate solution and an alkyl chloroformate derivative such as b nzyl chloroformate or methyl chloroformate to aff rd the corresponding benzyl (R^{14} = CH$_2$Ph) or methyl (R^{14} = CH$_3$) carbamate derivative 33. In the case where

35   33 is protected by an acyl derivative, it is necessary to remove the protecting group by appropriate means well-known to those skilled in the art to afford primary amine

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derivative **34**. Amine **34** is then treated with a dialkyl urea derivative, such as N,
N-dimethyl urea or N, N-dibenzyl urea in the presence of formaldehyde under
conditions pioneered by Knapp, *et al.*[2] to afford either the dimethyl (R = CH$_3$) or
dibenzyl (R = CH$_2$Ph) triazone derivative **35**. Triazone **35** can then be deprotonated

5   with a base such as n-butyllithium, lithium diisopropylamide (LDA) or lithium
bis(trimethylsilyl)amide in a solvent such as DMF or mixtures of DMF and THF at
temperatures in the range of -78° to -40°C to give a lithiated derivative which is
directly treated with commercially available (R)-(-)-glycidyl butyrate. The resulting
mixture is then warmed to ambient temperature to afford

10   (hydroxymethyl)oxazolidinone **36**.

         Chart XVII describes the conversion of triazone derivative **36** to compounds of
Formula v. As shown, triazone derivative **36** can be converted to
(acylaminomethyl)oxazolidinone **37** by means identical to those used to convert
compound **8** to **13** in Chart XII. The triazone group of **37** can be removed by

15   hydrolysis with aqueous hydrochloric acid or treatment with saturated ammonium
chloride solution to afford amine **38**. Compound **38** can be converted to a number of
carbonyl derviatives **39** (R = optionally substituted alkyl, alkoxy, alkylamino, etc.) by
treatment with various carbonyl derivatives, such as acyl chlorides, anhydrides,
alkyl and aryl chloroformates, isocyanates and the like, using appropriate bases and

20   catalysts in suitable solvents known to one skilled in the art. In addition, compound
38 can be converted into a number of alkyl derivatives **40** (R = optionally substituted
straight or branched chain alkyl) by treatment with an appropriate aldehyde or
ketone in the presence of hydrogen gas and a catalyst such as 10% palladium on
carbon or a reagent such as sodium cyanoborohydride in a protic solvent such as

25   methanol. Alternatively, **38** could be treated with an optionally substituted alkyl
halide in the presence of a base such as sodium carbonate in a suitable solvent such
as THF or acetonitrile, optionally in the presence of water. Thus prepared,
compounds **39** and **40** constitute examples of compounds of Formula v where n = 0.

         Chart XVIII describes the preparation of examples of compounds of structural

30   Formula v where R^3 = H, R^1 = NR^{8}R^9 and n = 1. As shown, pyrrolidine derivative
41, available by known methods,[1a, 3] optionally protected as either the
trifluoroacetamide (R = COCF$_3$) or th *tert*-butoxycarbonyl derivative (R = CO$_2$*t*-Bu)
is debenzylated by hydrogenolysis in the presence of a catalyst such as palladium
hydroxide on carbon, or 10% palladium n carbon in a suitable solvent such as

35   methanol to afford **42**. Pyrrolidine **42** can be allowed to react with a nitrobenzene
derivative such as **4** in the presence of a base, such as dibasic potassium phosphate,

in a solvent such as dimethyl sulfoxide (DMSO) to afford the aromatic displacement product 43. Aryl pyrrolidin 43 can be reduced by hydrogenation in the presence of a catalyst, such as 10% palladium on carbon or W-2 Raney nickel in a solvent such as THF or ethyl acetate to afford aniline derivative 44. Aniline derivative 44 is not

5 routinely isolated, but is generally treated directly with saturated sodium bicarbonate solution and an alkyl chloroformate such as benzyl or methyl chloroformate to afford the corresponding benzyl (R^{14} = CH_2Ph) or methyl (R^{14} =CH_3) carbamate derivative 45. In the case where 45 is protected as an acyl derivative, it is necessary to remove the protecting group by appropriate means well-

10 known to those skilled in the art to afford primary amine derivative 46. Amine 46 is then treated with a dialkyl urea derivative, such as N, N'-dimethyl urea or N, N'-dibenzyl urea in the presence of formaldehyde under conditions pioneered by Knapp, et al.[2] to afford either the dimethyl (R = CH_3) or the dibenzyl (R = CH_2Ph) triazone derivative 47. Triazone 47 can be deprotonated with a base such as n-butyllithium,

15 lithium diisopropylamide (LDA), or Lithium bis(trimethylsilyl)amide in a solvent such as DMF or mixtures of DMF and THF at temperatures in the range of -78° to -40°C to give a lithiated derivative which is directly treated with commercially available (R)-(-)-glycidyl butyrate. The resulting mixture is then warmed to ambient temperature to afford the (hydroxymethyl)oxazolidinone 48.

20 Chart XIX describes the conversion of triazone derivative 48 to compounds of structural Formula v. As shown, triazone derivative 48 can be converted to (acylaminomethyl)oxazolidinone 49 by means identical with those used to convert compound 8 to 13 in Chart XII. The triazone group of 49 can be removed by hydrolysis with aqueous hydrochloric acid solution or treatment with hot saturated

25 ammonium chloride solution to afford amine 50. Amine 50 can then be converted into a number of carbonyl derivatives 51 (R = optionally substituted alkyl, alkoxy, alkylamino, etc.) by treatment with various carbonyl derivatives, such as acyl chlorides, anhydrides, alkyl and aryl chloroformates, isocyanates, and the like, using appropriate bases and catalysts, in suitable solvents known to one skilled in the art.

30 In addition, amine 50 can be converted into a number of alkyl derivatives 52 (R = optionally substituted straight or branched chain alkyl) by treatment of 50 with an appropriate aldehyde or k tone in the presence of hydrogen gas and a catalyst such as 10% palladium on carbon or a reagent such as sodium cyanoborohydride in a protic solvent such as methanol. Alternatively, 50 could be treated with an

35 optionally substituted alkyl halide in the presence of a base such as sodium carbonate in a suitable solvent such as THF or acetonitrile, ptionally in the

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presence of water to afford 52. Thus prepared, compounds 51 and 52 constitute examples of oxazolidinone antibacterial agents of structural Formula v, where n =1.

It will be apparent to those skilled in the art that the described synthetic procedures are merely representative in nature and that alternative synthetic

5 processes are known, for example some of those described in the cited references.

Examples of pyrrolidinyl-phenyloxazolidinones that can be prepared as part of this invention are as follows:

1.   (S)-N-[[3-[3-Fluoro-4-(3-oxopyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

10

2.   (S)-N-[[3-[3-Fluoro-4-(3-oxo-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

3.   (S)-N-[[3-[3-Fluoro-4-(2,4-dimethyl-3-oxopyrrolidinyl)phenyl]-2-oxo-5-

15   oxazolidinyl]methyl]acetamide

4.   (S)-N-[[3-[3-Fluoro-4-(2,2-dimethyl-3-oxopyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

20 5.   (S)-N-[[3-[3-Fluoro-4-(4,4-dimethyl-3-oxopyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

6.   (S)-N-[[3-[3-Fluoro-4-(2,4-dimethyl-3-oxopyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

25

7.   (S)-N-[[3-[3-Fluoro-4-(3-isonitrosopyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

8.   (S)-N-[[3-[3-Fluoro-4-(O-methyl-3-isonitrosopyrrolidinyl)phenyl]-2-oxo-5-

30   oxazolidinyl]methyl]acetamide

9.   (S)-N-[[3-[3-Fluoro-4-(3-hydroxypyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

35

10.   (S)-N-[[3-[3-Fluoro-4-(cis-3-hydroxy-4-methylpyrrolidinyl)phenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide

11. (S)-N-[[3-[3-Fluoro-4-(*trans*-3-hydroxy-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

12. (S)-N-[[3-[3-Fluoro-4-(3-methoxypyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

13. (S)-N-[[3-[3-Fluoro-4-(*cis*-3,4-dihydroxypyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

14. (S)-N-[[3-[3-Fluoro-4-(*trans*-3,4-dihydroxypyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

15. (S)-N-[[3-[3-Fluoro-4-(3-(hydroxyacetylamino)pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

16. (S)-N-[[3-[3-Fluoro-4-[3-(phenylmethoxyacetylamino)pyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

17. (S)-N-[[3-[3-Fluoro-4-(3-(methoxyacetylamino)pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

18. (S)-N-[[3-[3-Fluoro-4-(3-(methoxycarbonylamino)pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

19. (S)-N-[[3-[3-Fluoro-4-(3-(ethoxycarbonylamino)pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

20. (S)-N-[[3-[3-Fluoro-4-(*cis*-3-(phenylmethoxyacetylamino)-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

21. (S)-N-[[3-[3-Fluoro-4-(*cis*-3-(hydoxyacetylamino)-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]m thyl]acetamide

22. (S)-N-[[3-[3-Fluoro-4-(*cis*-3-(methoxyacetylamino)-4-m thylpyrrolidinyl)-

-26-

phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

23. (S)-N-[[3-[3-Fluoro-4-(*cis*-3-(methoxycarbonylamino)-4-methylpyrrolidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

24. (S)-N-[[3-[3-Fluoro-4-(*cis*-3-(ethoxycarbonylamino)-4-methylpyrrolidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

25. (S)-N-[[3-[3-Fluoro-4-(*trans*-3-(phenylmethoxyacetylamino)-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

26. (S)-N-[[3-[3-Fluoro-4-(*trans*-3-(hydoxyacetylamino)-4-methylpyrrolidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

27. (S)-N-[[3-[3-Fluoro-4-(*trans*-3-(methoxyacetylamino)-4-methylpyrrolidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

28. (S)-N-[[3-[3-Fluoro-4-(*trans*-3-(methoxycarbonylamino)-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

29. (S)-N-[[3-[3-Fluoro-4-(*trans*-3-(ethoxycarbonylamino)-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

30. (S)-N-[[3-[3-Fluoro-4-(3-(phenylmethoxyacetylamino)methylpyrrolidinyl)-phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

31. (S)-N-[[3-[3-Fluoro-4-(3-(hydroxyacetylamino)methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

32. (S)-N-[[3-[3-Fluoro-4-(3-(methoxyacetylamino)methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

33. (S)-N-[[3-[3-Fluoro-4-(3-(methoxycarbonylamino)methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

34. (S)-N-[[3-[3-Fluoro-4-(3-(ethoxycarbonylamino)methylpyrrolidinyl)phenyl]-2-

-27-

oxo-5-oxazolidinyl]methyl]acetamide

35. (S)-N-[[3-[3-Fluoro-4-(cis-3-(phenylmethoxyacetylamino)methyl-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

36. (S)-N-[[3-[3-Fluoro-4-(cis-3-(hydroxyacetylamino)methyl-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

37. (S)-N-[[3-[3-Fluoro-4-(cis-3-(methoxyacetylamino)methyl-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

38. (S)-N-[[3-[3-Fluoro-4-(cis-3-(methoxycarbonylamino)methyl-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

39. (S)-N-[[3-[3-Fluoro-4-(cis-3-(ethoxycarbonylamino)methyl-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

40. (S)-N-[[3-[3-Fluoro-4-(trans-3-(phenylmethoxyacetylamino)methyl-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

41. (S)-N-[[3-[3-Fluoro-4-(trans-3-(hydroxyacetylamino)methyl-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

42. (S)-N-[[3-[3-Fluoro-4-(trans-3-(methoxyacetylamino)methyl-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

43. (S)-N-[[3-[3-Fluoro-4-(trans-3-(methoxycarbonylamino)methyl-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

44. (S)-N-[[3-[3-Fluoro-4-(trans-3-(ethoxycarbonylamino)methyl-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

45. (S)-N-[[3-[3-Fluoro-4-[trans-3-(phenylmethoxy)acetylamino-4-hydroxypyrrolidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

46. (S)-N-[[3-[3-Fluoro-4-(trans-3-(methoxyacetylamino)-4-

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hydroxypyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

47.   (S)-N-[[3-[3-Fluoro-4-(*trans*-3-(methoxycarbonylamino)-4-
       hydroxypyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

5

48.   (S)-N-[[3-[3-Fluoro-4-(*trans*-3-(ethoxycarbonylamino)-4-
       hydroxypyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Antibacterial Activity

      The oxazolidinone antibacterial agents of this invention have useful activity

10 against a variety of organisms. The *in vitro* activity of compounds of this invention

can be assessed by standard testing procedures such as the determination of

minimum inhibitory concentration (MIC) by agar dilution as described in "Methods

for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically"

(MFT) published Jan. 1983 by the National Committee for Clinical Laboratory

15 Standards, 771 East Lancaster Avenue, Villanova, Pennsylvania 19084, USA. The

activity of selected compounds of this invention against *Staphylococcus aureus* and

Streptococcus pneumoniae are shown in Table 1.

Tabl 1

Minimum Inhibitory Concentration (µg/mL)

Example No.	S. aureus UC® 9213	S. pneumoniae UC® 9912
1	4	2
2	4	2
3	16	8
4	1	0.5
5	4	1
6	8	4
7	8	2
8	32	8
9	8	2
10	2	1
11	4	2
12	8	2
13	16	2
14	4	1
15	16	2
16	8	1
vancomycin	1	0.5

Azetindinyl-Phenyloxazolidinones

EXAMPLE 1: (S)-N-[[3-[3-fluoro-4-(3-methoxy-1-azetidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1:   1-(diphenylmethyl)-3-methoxyazetidine

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A slurry of sodium hydride (0.440 g of a 60% dispersion in oil, 11.0 mmol) in dry tetrahydrofuran (125 mL) under nitrogen was cooled with an ice bath to 0 °C and treated with solid 1-(diphenylmethyl)-3-azetidinol (2.393 g, 10.0 mmol) over 5 min. After stirring 30 min at 0 °C, iodomethane (1.490 g, 0.654 mL, 10.5 mmol) was

5 added. When the addition was completed, the cooling bath was removed and the reaction mixture allowed to warm to ambient temperature overnight. The reaction mixture was poured into pH 7 phosphate buffer and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was

10 chromatographed over silica gel (300 mL) packed with dichloromethane, eluting with a gradient of 1-10% ethyl acetate/dichloromethane. Concentration of appropriate fractions afforded 2.081 g (82%) of the title compound as a pale yellow syrup with MS(EI) 253 (M$^+$).

Step 2:   3-fluoro-4-(3-methoxy-1-azetidinyl)nitrobenzene

15   A solution of 1-(diphenylmethyl)-3-methoxyazetidine (2.000 g, 7.91 mmol) in 25 % tetrahydrofuran/ethanol (100 mL) was treated with 5 N HCl (5.0 mL) and palladium hydroxide on carbon (Pearlman's catalyst, 0.500 g). The mixture was shaken on a Parr apparatus under 45 psi of H$_2$. After 16 h some starting material still remained by TLC analysis (silica gel, 6% acetonitrile/chloroform). An additional

20 0.500 g of Pearlman's catalyst was added and the hydrogenolysis continued a further 16 h, at which time the reaction appeared to be complete. The reaction mixture was filtered through Celite® and the filtrate concentrated under reduced pressure to an amber oil. This material was dissolved in dimethyl sulfoxide (30 mL) and treated with dipotassium hydrogen phosphate (6.88 g, 39.6 mmol) and 3,4-

25 difluoronitrobenzene (1.05 mL, 9.49 mmol). The reaction mixture was stirred at ambient temperature for 16 h, at which time TLC analysis (silica gel, 6% acetonitrile/chloroform) revealed the reaction to be complete. The reaction mixture was diluted with water (150 mL) and extracted with chloroform (3 x 40 mL). The combined organic extracts were washed with water (3 x 25 mL) and brine, dried over

30 sodium sulfate, filtered and concentrated *in vacuo* to give a crude product. Purification was accomplished by chromatography over silica gel (100 g), eluting with a gradient of 0-1% acetonitrile/chloroform. Concentration of appropriate fractions then afforded 1.50 g (84%) of the title compound as a bright yell w solid with mp 57.5-58 °C and MS(EI) 226 (M$^+$).

35 **Step 3:**   N-(carbobenzyloxy)-3-fluoro-4-(3-methoxy-1-azetidinyl)aniline
          A solution of 3-fluoro-4-(3-methoxy-1-azetidinyl)nitrobenzene (1.50 g, 6.64

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mmol) in 1:1 methanol/tetrahydrofuran (35 mL) was treated with 10% palladium on
carbon and then ammonium formate (1.26 g, 19.9 mmol) at room temperature. After
20 min the color of the reaction mixture changed from yellow to colorless. The
reaction mixture was filtered through Celite® and the filtrate concentrated under

5   reduced pressure. The recovered oil was immediately dissolved in 3:1 acetone/water
(25 mL) and treated with potassium carbonate (2.75 g, 19,9 mmol) and benzyl
chloroformate (1.31 mL, 8.30 mmol). After 30 min TLC analysis (6%
acetonitrile/chloroform) revealed the reaction to be complete. The reaction mixture
was extracted with chloroform (3 x 20 mL). The combined organic extracts were

10   washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to a
purple oil. This material was chromatographed over silica gel (100 g), eluting with a
gradient of 1-3% acetonitrile/chloroform, to give, after concentration of appropriate
fractions, 1.24 g (56%) of the title compound as an off-white solid with mp 95-96.5 °C
and MS(EI) 330 (M$^+$).

15   **Step 4:**   (R)-[3-[3-fluoro-4-(3-methoxy-1-azetidinyl)phenyl]-2-oxo-5-
oxazolidinyl]methanol

A solution of N-(carbobenzyloxy)-3-fluoro-4-(3-methoxy-1-azetidinyl)aniline
(0.865 g, 2.62 mmol) in dry tetrahydrofuran (10 mL) was cooled to -78 °C under a
nitrogen atmosphere and treated with n-butyllithium (1.65 mL of a 1.6 M solution in

20   hexanes, 2.65 mmol). After stirring at -78 °C for 15 min, the reaction mixture was
treated with (R)-glycidyl butyrate (0.374 mL, 2.65 mmol). The cooling bath was
then removed and the reaction mixture allowed to warm to ambient temperature.
After 1 h the reaction was judged complete by TLC analysis. The reaction mixture
was quenched by the addition of saturated aqueous ammonium chloride (0.5 mL)

25   and concentrated under reduced pressure to a yellow solid. Chromatography over
silica gel (10 g), eluting with a gradient of 1-2% methanol/chloroform afforded, after
concentration of appropriate fractions, 0.530 g (68%) of the title compound as an off-
white solid with mp 131-132 °C and MS(EI) 296 (M$^+$).

Step 5:   (R)-[[3-[3-fluoro-4-(3-methoxy-1-azetidinyl)phenyl]-2-oxo-5-
30   oxazolidinyl]methyl]methanesulfonate

A solution of (R)-[3-[3-fluoro-4-(3-methoxy-1-azetidinyl)phenyl]-2-oxo-5-
oxazolidinyl]methanol (0.492 g, 1.66 mmol) in dry dichloromethane (25 mL) under a
nitrogen atmosphere was cooled with an ice bath to 0 °C and treated with
triethylamine (0.254 mL, 1.83 mmol) and then methanesulfonyl chloride (0.141 mL,

35   1.83 mmol). After 1 h at 0 °C, TLC analysis (10% methanol/chloroform) revealed the
reaction to be complete. The reaction mixture was washed with water and brine,

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dried over sodium sulfate, filtered and concentrated *in vacuo* to a white solid.
Chromatography over silica gel (100 g), eluting with a gradient of 1-3%
methanol/chloroform afforded, after concentration of appropriate fractions, 0.601 g
(97%) of the title compound as a white solid with mp 122.5-123.5 °C and MS(EI) 374

5   (M⁺).

Step 6:   *(R)*-[[3-[3-fluoro-4-(3-methoxy-1-azetidinyl)phenyl]-2-oxo-5-
oxazolidinyl]methyl]azide

        (R)-[[3-[3-fluoro-4-(3-methoxy-1-azetidinyl)phenyl]-2-oxo-5-
oxazolidinyl]methyl]methanesulfonate (0.508 g, 1.36 mmol) was combined with

10   sodium azide (0.106 g, 1.63 mmol) in N,N-dimethylformamide (4 mL). The reaction
mixture was heated to 65 °C under a nitrogen atmosphere. After 2 hours, a small
amount of the starting mesylate still remained by TLC analysis (5%
methanol/chloroform). An additional 0.044 g of sodium azide was added and the
reaction heated for a further 1.5 h, at which time TLC revealed the reaction to be

15   complete. The reaction mixture was filtered and concentrated *in vacuo*. The residue
was chromatographed over silica gel (25 g), eluting with a gradient of 1-3%
methanol/chloroform. Appropriate fractions were combined and concentrated *in
vacuo* to furnish 0.426 g (98%) of the title compound as an off-white solid. An
analytical sample was prepared by recrystallization of this material from 3:1 ethyl

20   acetate/hexane to give a white solid with mp 111-112.5 °C and MS(EI) 321 (M⁺).

Step 7:   *(S)*-N-[[3-[3-fluoro-4-(3-methoxy-1-azetidinyl)phenyl]-2-oxo-5-
oxazolidinyl]methyl]acetamide

        A solution of *(R)*-[[3-[3-fluoro-4-(3-methoxy-1-azetidinyl)phenyl]-2-oxo-5-
oxazolidinyl]methyl]azide (0.393 g, 1.22 mmol) in 5:1 methanol/dichloromethane (20

25   mL) was treated with 10% palladium on carbon (0.030 g) under a nitrogen stream.
The atmosphere was then replaced with hydrogen (balloon). After stirring 3 hours
under hydrogen, the reduction was judged to be complete by TLC analysis (5%
methanol/chloroform). The reaction mixture was filtered through Celite® and
concentrated under reduced pressure. The crude 5-(aminomethyl)oxazolidinone was

30   dissolved in dichloromethane (15 mL) and treated with pyridine (0.118 mL, 1.46
mmol) and acetic anhydride (0.138 mL, 1.46 mmol) under a nitrogen atmosphere at
ambient temperature. After 2 h, the reaction was judged to be complete by TLC.
The reaction mixture was washed with water and brine, dried over sodium sulfate,
filtered and concentrated under reduced pressure. Chromatography over silica gel

35   (50 g), eluting with a gradient of 1-3% methanol/chloroform, afforded, after
conc ntration of appropriate fractions, 0.281 g (68%) of the title antibacterial agent

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as a white solid. An analytical sample, prepared by recrystallization from 2:1 ethyl acetate/hexane, was a white solid with mp 160-161.5 °C and MS(EI) 337 (M⁺).

EXAMPLE 2:   (S)-N-[[3-[3-fluoro-4-(3-hydroxy-1-azetidinyl)phenyl]-2-oxo-5-
oxazolidinyl]methyl]acetamide

Step 1:   3-fluoro-4-(3-hydroxy-1-azetidinyl)nitrobenzene

1-(Diphenylmethyl)-3-azetidinol hydrochloride (2.000 g, 7.29 mmol) was dissolved in methanol (75 mL) and treated with 6N HCl (1.20 mL, 7.29 mmol). Palladium hydroxide on carbon (0.200 g) was then added under a nitrogen stream. The reaction mixture was then shaken on a Parr apparatus under 40 psi of H_2. After 16 h, TLC analysis (5% methanol/chloroform) revealed the starting material was consumed. The reaction mixture was filtered through Celite® and concentrated under reduced pressure to an amber oil. This material was dissolved in dimethylsulfoxide (29 mL) and the atmosphere replaced with nitrogen. Dipotassium hydrogen phosphate (5.07 g, 29.2 mmol) was added followed by 3,4-difluoronitrobenzene (0.966 mL, 8.75 mmol). The mixture was stirred at ambient temperature under nitrogen. After 3 h, TLC analysis (5% methanol/chloroform) revealed the reaction to be complete. The reaction mixture was diluted with water (250 mL) and extracted with chloroform (4 x 50 mL). The combined organic extracts were washed with water (2 x 50 mL) and brine, dried over sodium sulfate, filtered and concentrated in vacuo to give a yellow solid. Chromatography over silica gel (100 g), eluting with a gradient of 3-7% acetonitrile/chloroform afforded, after concentration of appropriate fractions, 1.00 g (65%) of the title compound as an orange solid with mp 130.5-132 °C and MS(EI) 212 (M⁺).

Step 2:   4-[3-[(tert-butyldimethylsilyl)oxy]-1-azetidinyl]-3-fluoronitrobenzene

A solution of 3-fluoro-4-(3-hydroxy-1-azetidinyl)nitrobenzene (5.51 g, 26.0 mmol) in N,N-dimethylformamide (104 mL) under nitrogen was cooled to 0 °C with an ice bath and treated with imidazole (1.86 g, 27.3 mmol) and then tert-butyldimethylsilyl chloride (4.12 g, 27.3 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature overnight. TLC analysis (5% methanol/chloroform) at this time revealed a small amount of starting material still remained. An additional amount of tert-butyldimethylsilyl chloride (0.392 g) was added. After stirring overnight, TLC analysis indicated th reaction was complete. The reaction mixture was diluted with water (500 mL) and extracted with dichloromethane (4 x 70 mL). The combined organic extracts w re washed with water and brine, dried over sodium sulfate, filtered and concentrated under reduced

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pressure to a yellow solid. Chromatography over silica gel (200 g), eluting with 5%
and 10% ethyl acetate/hexane, afforded, after concentration of appropriate fractions,
6.30 g (74%) of the title compound as a yellow solid with mp 98.5-99.5 °C and
MS(EI) 326 (M⁺).

5   **Step 3:**   N-(carbobenzyloxy)-4-[3-[(*tert*-butyldimethylsilyl)oxy]-1-azetidinyl]-3-
fluoroaniline

          4-[3-[(*tert*-Butyldimethylsilyl)oxy]-1-azetidinyl]-3-fluoronitrobenzene (1.00 g,
3.07 mmol) was combined with 10% palladium on carbon (0.100 g) in 3:1
tetrahydrofuran/water (25 mL) under a nitrogen atmosphere. The atmosphere was

10   replaced with hydrogen (balloon) by repeated evacuation and filling. After 2 h the
initial yellow color of the reaction solution disappeared and TLC analysis (15% ethyl
acetate/hexane) revealed the reduction to be complete. The reaction mixture was
filtered through Celite® and the filtrate immediately placed under a nitrogen
atmosphere and treated with sodium bicarbonate (1.41 g, 16.8 mmol) and benzyl

15   chloroformate (0.528 mL, 3.69 mmol). After 30 min at ambient temperature, TLC
analysis (15% ethyl acetate/hexane) indicated the reaction was complete. The
reaction mixture was concentrated under reduced pressure to an off-white solid.
Cromatography over silica gel (125 g), eluting with a gradient of 5-30% ethyl
acetate/hexane, afforded, after concentration of appropriate fractions, 0.565 g (43%)

20   of the title compound as a white solid with mp 91-93 °C and MS(EI) 430 (M⁺).

       Step 4:   (*R*)-[3-[4-[3-[(*tert*-butyldimethylsilyl)oxy]-1-azetidinyl]-3-fluorophenyl]-
2-oxo-5-oxazolidinyl]methanol

       A solution of N-(carbobenzyloxy)-4-[3-[(*tert*-butyldimethylsilyl)oxy]-1-azetidinyl]-3-
fluoroaniline (6.30 g, 14.7 mmol) in dry tetrahydrofuran (100 mL) under a nitrogen

25   atmosphere was cooled to -78 °C and treated with *n*-butyllithium (9.16 mL of a 1.6
M solution in hexanes, 14.7 mmol). When the addition was complete, the reaction
mixture was stirred at -78 °C for 15 min and then treated with (*R*)-glycidyl butyrate
(2.21 mL, 14.7 mmol). After completion of the addition, the cooling bath was
removed and the reaction mixture allowed to stir at ambient temperature for 1.5 h.

30   After this time, saturated aqueous ammonium chloride (20 mL) was added. After 3
min, saturated aqueous sodium bicarbonate (10 mL) was added to the reaction
mixture and the organic solvent removed by rotary evaporation under reduced
pressure. Dichloromethane (100 mL) was added and the mixture washed with water
and brine. The organic lay r was dried over sodium sulfate, filtered and

35   concentrated *in vacuo*. Chromatography over silica gel (200 g), eluting with a
gradient of 1-3% methanol/chloroform, afforded, after concentration of appropriate

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fractions, 4.39 g (75%) of the title compound as an off-white solid with mp 183-186
°C and MS(EI) 396 (M⁺).

Step 5: (R)-[[3-[4-[3-[(tert-butyldimethylsilyl)oxy]-1-azetidinyl]-3-fluorophenyl]-
2-oxo-5-oxazolidinyl]methyl]methanesulfonate

5   Crude (R)-{3-[4-[3-[(tert-butyldimethylsilyl)oxy]-1-azetidinyl]-3-fluorophenyl]-
2-oxo-5-oxazolidinyl]methanol (5.38 g, 13.6 mmol) was dissolved in dry
dichloromethane (70 mL), cooled to 0 °C with an ice bath, and treated with
triethylamine (2.08 mL, 14.9 mmol) and then methanesulfonyl chloride (1.15 mL,
14.9 mmol). After 30 min at 0 °C, the reaction was complete by TLC analysis (5%
10   methanol/chloroform). The reaction mixture was washed with saturated aqueous
sodium bicarbonate, water and brine, dried over sodium sulfate, filtered and
concentrated under reduced pressure to an off-white solid. An analytical sample,
prepared by triturating the crude product with isopropanol and diethyl ether,
followed by filtration and drying in vacuo, afforded an off-white solid with mp 142-
15   145 °C and MS(EI) 474 (M⁺).

Step 6: (R)-[[3-[4-[3-[(tert-butyldimethylsilyl)oxy]-1-azetidinyl]-3-fluorophenyl]-
2-oxo-5-oxazolidinyl]methyl]azide

           Crude (R)-[[3-[4-[3-[(tert-butyldimethylsilyl)oxy]-1-azetidinyl]-3-fluorophenyl]-
2-oxo-5-oxazolidinyl]methyl]methanesulfonate (9.42 mmol) was dissolved in dry N,N-
20   dimethylformamide (50 mL) and treated with sodium azide (4.42 g, 68.0 mmol) at
ambient temperature. The reaction mixture was warmed to 65 °C under nitrogen
for 4 h. TLC analysis (5% methanol/chloroform) at this time revealed the reaction to
be complete. The reaction mixture was diluted with ethyl acetate (100 mL) and
washed with water (3 x 25 mL) and brine, dried over sodium sulfate, filtered and
25   concentrated in vacuo to an amber solid. Chromatography over silica gel (125 g),
eluting with a gradient of 10-20% ethyl acetate/hexane, afforded, after concentration
of appropriate fractions, 2.21 g (56% for 3 steps) of the title azide as a white solid
with mp 121-122.5 °C and MS(EI) 421 (M⁺).

Step 7: (S)-N-[[3-[4-[3-[(tert-butyldimethylsilyl)oxy]-1-azetidinyl]-3-
30   fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

           A solution of (R)-[[3-[4-[3-[(tert-butyldimethylsilyl)oxy]-1-azetidinyl]-3-
fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]azide (2.04 g, 4.85 mmol) in 1:1 ethyl
acetate/methan l (200 mL) was treated with 10% palladium on carbon (0.300 g)
under a nitrogen stream. The atmosphere was then replaced with H₂ (balloon) by
35   repeated evacuation and filling. After 3 h, TLC analysis (5% methanol/chloroform)
revealed the reduction to be complete. The reaction mixture was filtered through

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Celite® and the filtrate concentrated under reduced pressure to a white solid. The crude 5-(aminomethyl)oxazolidinone was dissolved in dichloromethane (100 mL), cooled to 0 °C under a nitrogen atmosphere, and treated with pyridine (0.431 mL, 5.33 mmol) and acetic anhydride (0.503 mL, 5.33 mmol). After 30 min at 0 °C, the

5   acetylation was complete by TLC (5% methanol/chloroform). The reaction mixture was washed with water and brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give the crude product as a tan solid. Chromatography over silica gel (125 g), eluting with a gradient of 1-3% methanol/chloroform, afforded, after concentration of appropriate fractions, 1.77 g (84%) of the title compound as a

10 white solid with mp 183.5-184 °C and MS(EI) 437 (M$^+$).

Step 8:   (S)-N-[[3-[3-fluoro-4-(3-hydroxy-1-azetidinyl)phenyl]-2-oxo-5-
             oxazolidinyl]methyl]acetamide

An acetonitrile (55 mL) solution of (S)-N-[[3-[4-[3-[(*tert*-butyldimethylsilyl)oxy]-1-azetidinyl]-3-fluorophenyl]-2-oxo-5-

15 oxazolidinyl]methyl]acetamide (1.23 g, 2.81 mmol) in a polypropylene bottle was treated with 38% aqueous hydrofluoric acid (15 mL) at ambient temperature. TLC analysis revealed the deprotection to be complete after 3 h. The reaction mixture was diluted with water (15 mL) and neutralized with solid sodium bicarbonate. Additional water was added (50 mL) and the mixture extracted with chloroform.

20 The combined organic extracts were washed with water and brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give the title oxazolidinone antibacterial agent as an off-white solid with mp 174-177 °C and MS(EI) 323 (M$^+$).

EXAMPLE 3:   (S)-N-[[3-[3-fluoro-4-[3-[N-(2-fluoroethyl)-N-methylamino]-1-
25 azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

Step 1:   1-(Diphenylmethyl)-3-[N-(2-fluoroethyl)-N-methylamino]azetidine

1-(Diphenylmethyl)-3-(methylamino)azetidine (5.00 g, 19.8 mmol) was combined with potassium carbonate (16.4 g, 119 mmol) and 2-fluoroethyl tosylate (6.50 g, 29.8 mmol) in 6% water/acetonitrile (200 mL). The mixture was heated to

30 reflux temperature under a nitrogen atmosphere. After 3 h at reflux, TLC analysis (5% methanol/chloroform) revealed a small amount of starting material remained. An additional 1.8 g of 2-fluoroethyl tosylate was added and the reaction mixture refluxed a furhter 2 h. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. Chromatography over silica gel (200 g),

35 eluting with a gradient of 1-5% acetonitrile/chloroform, afforded, after concentration of appropriate fractions, 4.07 g (69%) of the title compound as an amber syrup with

IR 1598, 1452, 1362, 1029 cm^{-1}.

Step 2:   3-fluoro-4-[3-[N-(2-fluoroethyl)-N-methylamino]-1-
               azetidinyl]nitrobenzene

A Parr bottle was charged with 1-(Diphenylmethyl)-3-[N-(2-fluoroethyl)-N-

5   methylamino]azetidine (3.88 g, 13.0 mmol) and 25% tetrahydrofuran/ethanol (130

mL). Palladium hydroxide on carbon (1.9 g) was then added under a nitrogen

stream. The mixture was then shaken on a Parr apparatus under 45 psi of H$_2$.

After 20 hours, TLC analysis (5% methanol/chloroform) reavealed the hydrogenolysis

to be complete. The reaction mixture was filtered through Celite® and concentrated

10 under reduced pressure to a colorless oil. This material was dissolved in dimethyl

sulfoxide (50 mL) and treated with dipotassium hydrogen phosphate (13.6 g, 78.0

mmol) followed by 3,4-difluoronitrobenzene (1.72 mL, 15.6 mmol). The reaction

mixture was then stirred at ambient temperature and reaction progress monitored

by TLC analysis (5% methanol/chloroform). After 4 hours, the reaction mixture was

15 added to H$_2$O (500 mL) and extracted with dichloromethane (4 x 75 mL). The

combined organic extracts were washed with water and brine, dried over sodium

sulfate, filtered and concentrated *in vacuo* to a yellow syrup. Chromatography over

silica gel (200 g), eluting with a gradient 0-2.5% acetonitrile/dichloromethane,

afforded, after concentration of appropriate fractions, 2.87 g (81%) of the title

20 compound as a yellow solid with mp 46.5-48 °C and MS(FAB) 272 (M + H)$^+$.

Step 3:   N-(carbobenzyloxy)-3-fluoro-4-[3-[N-(2-fluoroethyl)-N-methylamino]-1-
               azetidinyl]aniline

A solution of 3-fluoro-4-[3-[N-(2-fluoroethyl)-N-methylamino]-1-

azetidinyl]nitrobenzene (2.66 g, 9.82 mmol) in 2:1 tetrahydrofuran/water (50 mL)

25 and acetic acid (2.0 mL) was treated with 10% palladium/carbon under a nitrogen

stream. The atmosphere was replaced with H$_2$ (balloon) by repeated evacuation and

filling and the reaction mixture stirred under H$_2$ overnight. TLC analysis (6%

acetonitrile/chloroform) at this time revealed the reduction to be complete. The

reaction mixture was filtered through Celite®. Exposure to air was minimized since

30 a purple color rapidly developed under these conditions. The filtrate was cooled

with an ice bath to ca. 0 °C and treated with potassium carbonate (6.8 g, 49 mmol)

and benzylchloroformate (1.63 mL, 10.3 mmol). The reaction mixture was stirred at

ca. 0°C for 1 h and then warmed to room temperature over 30 min. TLC analysis

(6% acetonitrile/chloroform) at this time revealed the reaction to be complete. The

35 reaction mixture was diluted with water (200 mL) and extracted with chloroform (3

x 75 mL). The combined organic extracts were washed with water and brine, dried

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over sodium sulfate, filtered and concentrated *in vacuo* to a dark amber syrup. Chromatography over silica gel (200 g), eluting with a gradient of 1-3% methanol/chloroform, afforded, after concentration of appropriate fractions, 3.71 g (100%) of the title compound as an amber syrup. An analytical sample was

5 prepared by an additional chromatographic purification to give a light amber solid with mp 57-59 °C and MS(EI) 375 (M⁺).

Step 4: (R)-N-[3-[3-fluoro-4-[3-[N-(2-fluoroethyl)-N-methylamino]-1-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methanol

A solution of N-(carbobenzyloxy)-3-fluoro-4-[3-[N-(2-fluoroethyl)-N-

10 methylamino]-1-azetidinyl]aniline (3.38 g, 9.01 mmol) in dry tetrahydrofuran (40 mL) under nitrogen was cooled to -78°C and treated with *n*-butyllithium (5.69 mL of a 1.6 M solution in hexane, 9.10 mmol). The reaction mixture was warmed to -40°C and then recooled to -78 °C and treated with (R)-glycidyl butyrate (1.29 mL, 9.10 mmol). When the addition was completed, the reaction mixture was allowed to

15 warm to ambient temperature. After 1 h, the reaction appeared to be complete by TLC analysis (5% methanol/chloroform). The reaction mixture was quenched with saturated aqueous ammonium chloride (1 mL), diluted with water (100 mL), and extracted with chloroform (3 x 50 mL). The combined organic extracts were washed with water and brine, dried over sodium sulfate, filtered and concentrated under

20 reduced pressure to an amber syrup. Chromatography over silica gel (200 g), eluting with a gradient of 1-4% methanol/chloroform, afforded, after concentration of approriate fractions, 1.69 g (55%) of the title compound as an off-white solid with mp 124-125 °C and MS(EI) 341 (M⁺).

Step 5: (R)-[[3-[4-[3-[N-(2-fluoroethyl)-N-methylamino]-1-azetidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate

25

A solution of (R)-N-[3-[3-fluoro-4-[3-[N-(2-fluoroethyl)-N-methylamino]-1-azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methanol (1.40 g, 4.11 mmol) in dry dichloromethane (16 mL) was treated with triethylamine (0.628 mL, 4.52 mmol) and then cooled to 0 °C under a nitrogen atmosphere. Methanesulfonyl chloride (0.348

30 mL, 4.52 mmol) was then added and the mixture stirred at 0 °C. TLC analysis (5% methanol/chloroform) after 2 h revealed a small amount of starting material still remained. An additional portion of methanesulfonyl chloride (0.100 mL, 1.30 mmol) was added and the reaction continued a further 1 h at 0 °C. The reaction mixture was washed with saturated aqueous sodium bicarbonate, dried ov r sodium sulfate,

35 filtered and concentrated *in vacuo* to give 1.88 g (100%) of the title compound as a light orange solid. ¹H NMR analysis indicated this material was of high quality.

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An analytical sample was prepared by chromatographing 200 mg of the crude product over silica gel (10 g), eluting with a gradient of 1-4% m thanol/chloroform, to afford, after concentration of appropriate fractions, 99 mg of the title compound as an off-white solid with mp 96.5-98 °C and MS(EI) 419 (M$^+$).

5   **Step 6:**   (R)-[[3-[4-[3-[N-(2-fluoroethyl)-N-methylamino]-1-azetidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]azide

A solution of (R)-[[3-[4-[3-[N-(2-fluoroethyl)-N-methylamino]-1-azetidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate (1.65 g, 3.94 mmol) in dry N,N-dimethylformamide (15 mL) was treated with solid sodium azide (0.768 g,

10   11.8 mmol). The reaction mixture was then heated to 65 °C under a nitrogen atmosphere. After 3 h, TLC analysis (5% methanol/chloroform) revealed a small amount of starting mesylate still remained. An additional portion of sodium azide (0.256 g, 3.94 mmol) was added and the reaction mixture heated at 65 °C for 1h. The reaction mixture was cooled to ambient temperature, filtered and concentrated

15   under reduced pressure. The residue was chromatographed over silica gel (100 g), eluting with a gradient of 1-4% methanol/chloroform, to afford, after concentration of appropriate fractions, 1.24 g (86%) of the title compound as an off-white solid with mp 60-63 °C and MS(EI) 366 (M$^+$).

      Step 7:   (S)-N-[[3-[3-fluoro-4-[3-[N-(2-fluoroethyl)-N-methylamino]-1-

20   azetidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of (R)-[[3-[4-[3-[N-(2-fluoroethyl)-N-methylamino]-1-azetidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]azide (1.14 g, 3.11 mol) in methanol (20 mL) was treated with 10% palladium/carbon (0.114 g) under a nitrogen stream. The atmosphere was replaced with H$_2$ (balloon) by repeated evacuation and filling. After

25   2.5 h, TLC analysis (5% methanol/chloroform) revealed the reduction to be complete. The reaction mixture was filtered through Celite$^®$ and the filtrate concentrated *in vacuo* to an off-white solid. This material was dissolved in dichloromethane (20 mL) and treated with pyridine (0.264 mL, 3.27 mmol) and acetic anhydride (0.309 mL, 3.27 mmol) under nitrogen. After 30 min TLC analysis (5% methanol/chloroform)

30   indicated the acetylation to be complete. the reaction mixture was washed with water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give an amber oil. Chromatography over silica gel (125 g), eluting with a gradient of 1-4% methanol/chloroform, aff rded, after concentration of appropriate fractions, 0.892 g (75%) of the title oxazolidinone antibact rial agent as an off-white

35   solid with mp 125.5-127 °C and MS(EI) 382 (M$^+$).

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EXAMPLE 4:   (S)-N-[[3-[3-fluoro-4-(3-oxo-1-azetidinyl)phenyl]-2-oxo-5-
oxazolidinyl]methyl]acetamide

A solution of (S)-N-[[3-[3-fluoro-4-(3-hydroxy-1-azetidinyl)phenyl]-2-oxo-5-
oxazolidinyl]methyl]acetamide (EXAMPLE 2, 0.440 g, 1.36 mmol) in 10%
5 acetonitrile/dichloromethane (100 mL) was treated with powdered 4 angstrom
molecular sieves (0.682 g), 4-methylmorpholine N-oxide (0.319 g, 2.72 mmol) and
then tetra-n-propylammonium perruthenate (0.024 g, 0.068 mmol) at ambient
temperature. After stirring 1.5 hours at ambient temperature, TLC analysis (10%
methanol/chloroform) revealed a small amount of starting alcohol still remained.
10 The addition of more 4-methylmorpholine N-oxide did not consume the starting
material. The reaction mixture was concentrated under reduced pressure to a dark
purple solid which was then chromatographed over silica gel (20 g), eluting with a
gradient of 1-3.5% methanol/chloroform, to afford, after concentration of appropriate
fractions, 0.204 g (47%) of the title oxazolidinone antibacterial agent as a white solid
15 with mp 192-193 °C and MS(EI) 321 (M$^+$).

EXAMPLE 5:   (S)-N-[[3-[3-fluoro-4-[3-(methoxyimino)-1-azetidinyl]phenyl]-2-
oxo-5-oxazolidinyl]methyl]acetamide

A solution of (S)-N-[[3-[3-fluoro-4-(3-oxo-1-azetidinyl)phenyl]-2-oxo-5-
20 oxazolidinyl]methyl]acetamide (EXAMPLE 4, 0.200 g, 0.623 mmol) in 5%
methanol/dichloromethane (10 mL) was treated with pyridine (0.201 mL, 2.49 mmol)
and then methoxylamine hydrochloride (0.052 g, 0.623 mmol) at ambient
temperature. After 1.5 hours, TLC analysis (10% methanol/chloroform) revealed the
reaction to be complete. The reaction mixture was concentrated under reduced
25 pressure to a white solid. Cromatography over silica gel (10 g), eluting wiht a
gradient of 1-3% methanol/chloroform, afforded, after concentration of appropriate
fractions, 0.204 g (94%) of the title oxazolidinone antibacterial agent as an off-white
solid. Another synthetic run provided material with mp 189-192 °C and MS(EI) 350
(M$^+$).

30

EXAMPLE 6:   (S)-N-[[3-[3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)phenyl]-2-
oxo-5-oxazolidinyl]methyl]acetamide
Step 1:   1-(diphenylmethyl)-3-methoxy-3-methylazetidine
A slurry of 1-(diphenylmethyl)-3-methyl-3-azetidinol hydrochloride (5.00 g,
35 17.2 mmol) in dry tetrahydrofuran (200 mL) was cooled with an ice bath to 0 °C and
treated with sodium hydride (2.10 g of a 60% dispersion in oil, 51.8 mmol) under

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nitrogen. The cooling bath was removed and the mixture warmed to reflux temperature for 15 min. After cooling to room temperature, iodomethane (7.40 g, 3.22 mL, 51.8 mmol) was added. When the addition was completed, the reaction mixture was heated to reflux temperature for 15 hours. TLC analysis (9:1 hexane

5   /ethyl acetate) revealed the methylation to be complete. The reaction mixture was quenched with saturated aqueous ammonium chloride. The mixture was transferred to a separatory funnel with ethyl acetate and water and then extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude

10   product was chromatographed over silica gel , eluting with 9:1 ethyl acetate/hexane. Concentration of appropriate fractions afforded 2.30 g (50%) of the title compound as a colorless oil with MS(EI) 267 (M⁺).

Step 2:   3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)nitrobenzene

A solution of 1-(diphenylmethyl)-3-methoxy-3-methylazetidine (2.20 g, 8.2

15   mmol) in 25% tetrahydrofuran/ethanol was treated with glacial acetic acid (1.60 g, 1.50 mL, 24.7 mmol) and then palladium hydroxide on carbon (0.220 g) under a nitrogen stream. The reaction mixture was shaken on a Parr apparatus under 35 psi of H_2. At this time TLC analysis (9:1 hexane/ethyl acetate) revealed the reaction to be complete. The mixture was filtered through Celite® (ethyl acetate wash) and

20   the filtrate concentrated *in vacuo* to give an oil. This material was dissolved in dimethyl sulfoxide (15 mL) and the solution treated with dipotassium hydrogen phosphate (8.60 g, 49.2 mmol) and 3,4-difluoronitrobenzene (1.30 g, 0.886 mL, 8.0 mmol) at ambient temperature. The yellow reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for 18 hours. The reaction mixture was

25   diluted with water and extracted with dichloromethane. The combined organic extracts were washed with water and brine, dried over sodium sulfate, filtered and dried *in vacuo* to give a yellow solid. Chromatography over silica gel, eluting with 8:1 hexane/ethyl acetate, afforded, after concentration of appropriate fractions, 1.80 g (90%) of the title compound as a yellow solid with mp 110-111 °C and MS(EI) 240

30   (M⁺).

Step 3:   N-(carbobenzyloxy)-3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)aniline

A solution of 3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)nitrobenzene (1.60 g, 6.7 mmol) in 25% tetrahydrofuran/methanol (35 mL) was d gassed by repeated evacuati n and filling with N_2 and th n treated with 10% palladium/carbon (0.160

35   g). Ammonium formate (2.10 g, 33.3 mmol) was then added and the mixture degass d a final time. The reaction mixture was stirred at ambient temperature for

20 minutes, during which time the yellow reaction mixture became colorless. TLC analysis (2:1 hexane/ethyl acetate) revealed the reduction to be complete. The reaction mixture was filtered through Celite® (dichloromethane and methanol wash) and the filtrate concentrated *in vacuo* to give a purple gum that was immediately

5   dissolved in 1:1 acetone/water (30 mL) under N_2. The mixture was cooled with an ice bath to 0 °C and treated with sodium bicarbonate (1.10 g, 13.4 mmol) and benzyl chloroformate (1.20 g, 1.00 mL, 7.37 mmol). The cooling bath was allowed to dissipate over a 3 h period. After stirring a further 2 h at ambient temperature, the reaction mixture was transferred to a separatory funnel with dichloromethane (50

10 mL). The organic phase was separated, washed with water, dried over sodium sulfate, filtered and concentrated *in vacuo* to give a purple oil. Chromatography over silica gel, eluting with 6:1 hexane/ethyl acetate, afforded, after concentration of appropriate fractions, 2.04 g (89%) of the title compound as a viscous oil which solidified on standing to a waxy solid with mp 73-75 °C and MS(EI) 344 (M^+).

15 **Step 4:**   (*R*)-[3-[3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)phenyl]-2-oxo-5-
                      oxazolidinyl]methanol

         A solution of N-(carbobenzyloxy)-3-fluoro-4-(3-methoxy-3-methyl-1-
azetidinyl)aniline (1.85 g, 5.4 mmol) in dry tetrahydrofuran (20 mL) was cooled to -
78 °C with a dry ice/acetone bath and treated with *n*-butyllithium (3.50 mL of a 1.6

20 M solution in hexane, 5.7 mmol) via syringe. After 5 min at this temperature, (*R*)-
glycidyl butyrate (0.823 g, 0.807 mL, 5.7 mmol) was added via syringe and the
reaction mixture left overnight, with gradual dissipation of the cooling bath. TLC
analysis (5% methanol/chloroform) revealed the starting Cbz derivative was
consumed. the reaction mixture was concentrated under reduced pressure to a waxy

25 orange solid. The residue was dissolved in 20% methanol/dichloromethane, washed
sequentially with saturated ammonium chloride, saturated sodium bicarbonate and
brine. The organic layer was dried over sodium sulfate, filtered and concentrated *in
vacuo* to give a crude product. Radial chromatography over silica gel, eluting with
2%, 3% and then 5% methanol/chloroform, afforded, after concentration of

30 appropriate fractions, 0.811 g (48%) of the title compound as a colorless gum which
was very clean by ^{1}H NMR analysis. An analytical sample was prepared by
recrystallization from dichloromethane/diethyl ether to give a white solid with mp
113-114 °C and MS(EI) 310 (M^+).

     Step 5:   (*R*)-[[3-[3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)phenyl]-2-oxo-5-

35   oxazolidinyl]methyl]methanesulfonate

         A solution of (*R*)-[3-[3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)phenyl]-2-

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oxo-5-oxazolidinyl]methanol (0.700 g, 2.25 mmol) in dry dichloromethane (10 mL) was cooled to 0 °C with an ice bath. Triethylamine (0.250 g, 0.345 mL, 2.48 mmol) and then methanesulfonyl chloride (0.271 g, 0.183 mL, 2.37 mmol) were then added and the reaction mixture stirred under N_2 while the cooling bath dissipated. After 3

5   h TLC analysis (5% methanol/chloroform) revealed the mesylation to be essentially complete. The reaction mixture was diluted with additional dichloromethane and washed with 0.5 N hydrochloric acid, saturated aqueous sodium bicarbonate and brine. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. Radial chromatography over silica gel, eluting with 3% methanol/chloroform,

10   afforded, after concentration of appropriate fractions, 0.022 g of recovered starting alcohol and 0.700 g (80%) of the title compound as a white solid with MS(EI) 388 (M^+).

Step 6:   (S)-N-[[3-[3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

15   A mixture of (R)-[[3-[3-fluoro-4-(3-methoxy-3-methyl-1-azetidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate (0.680 g, 1.75 mmol) in 2:1 ammonium hydroxide/isopropanol (30 mL) was heated to reflux (dry-ice condenser). TLC analysis (5% methanol/chloroform) after 7 hours revealed mostly starting material. The reaction was continued for an additional 46 hours. After cooling to ambient

20   temperature, TLC indicated that the starting mesylate was essentially consumed. The reaction mixture was transferred to a separatory funnel, along with dichloromethane (100 mL), and washed with water. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude 5-(aminomethyl)oxazolidinone was dissolved in dry dichloromethane (10 mL), cooled to

25   0 °C with an ice bath, and treated with pyridine (0.698 g, 0.708 mL, 8.75 mmol) and acetic anhydride (0.357 g, 0.330 mL, 3.50 mmol). The cooling bath was then removed and the reaction mixture stirred at ambient temperature overnight. The reaction mixture was diluted with additional dichloromethane (60 mL) and washed with 5% aqueous hydrochloric acid, saturated aqueous sodium carbonate, water and

30   brine. The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a crude gum. Radial chromatography over silica gel, eluting with 1%, 2% and 4% methanol/chloroform afforded, after concentration of appropriate fractions, 0.481 g (78%) of the titl oxazolidinone antibacterial agent as a white foamy solid. A lyophilized sample had mp 132-134 °C and MS(EI) 351 (M^+).

35

EXAMPLE 7:   (S)-N-[[3-[3-fluoro-4-(3-hydroxy-3-methyl-1-azetidinyl)phenyl]-2-

oxo-5-oxazolidinylmethyl)acetamide

Step 1:   3-fluoro-4-(3-hydroxy-3-methyl-1-azetidinyl)nitrobenzene

A solution of 1-(diphenylmethyl)-3-methyl-3-azetidinol hydrochloride (3.00 g, 10.4
mmol) in 2:1 methanol/tetrahydrofuran (60 mL) was treated with triethylamine

5   (1.00 g, 1.40 mL, 10.4 mmol) and then palladium hydroxide/carbon (0.300 g) under a
N_2 stream. The mixture was shaken on a Parr apparatus under 40 psi H_2. TLC
analysis (2:1 hexane/ethyl acetate) after 2.5 h revealed the hydrogenolysis to be
complete. The reaction mixture was filtered through Celite® (dichloromethane
wash) and the filtrate concentrated under reduced pressure to give an oil which was

10   immediately taken-up in dry dimethyl sulfoxide (15 mL) and treated with
dipotassium hydrogen phosphate (3.40 g, 19.8 mmol) and 3,4-difluoronitrobenzene
(1.60 g, 1.10 mL, 9.9 mmol) at ambient temperature under N_2. After stirring 16
hours at his temperature, TLC analysis (2:1 hexane/ethyl acetate) revealed the
reaction to be essentially complete. The reaction mixture was transferred to a

15   separatory funnel along with dichloromethane (100 mL) and water (150 mL). After
shaking, the organic phase was separated. The aqueous phase was back-extracted
with dichloromethane and the combined organic extracts washed with water, dried
over sodium sulfate, filtered and concentrated *in vacuo* to an oil. Chromatography
over silica gel, eluting with 3:1 hexane/ethyl acetate, afforded, after concentration of

20   appropriate fractions, 2.15 g (98%) of the title compound as an orange solid with mp
109-110 °C and MS(EI) 226 (M^+).

Step 2:   4-[3-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-1-azetidinyl]-3-
                fluoronitrobenzene

A solution of 3-fluoro-4-(3-hydroxy-3-methyl-1-azetidinyl)nitrobenzene (1.80 g,

25   8.0 mmol) in dry N,N-dimethylformamide (15 mL) was cooled to 0 °C with an ice
bath and then treated with imidazole (0.572 g, 8.4 mmol) and *tert*-butyldimethylsilyl
chloride (1.30 g, 8.4 mmol) under N_2. The reaction mixture was stirred overnight
with gradual dissipation of the cooling bath. The reaction mixture was then
transferred to a separatory funnel, along with water and 1:1 hexane/diethyl ether.

30   After shaking, the layers were separated and the aqueous phase back-extracted with
additional 1:1 hexane/diethyl ether. The combined organic extracts were washed
with water and brine, dried over sodium sulfate, filtered and concentrated *in vacuo*
to give an oil. Chromatography over silica gel, eluting with 3% diethyl ether/hexane
and then 1:1 hexane/ethyl acetate, afforded, after concentration of appropriate

35   fractions, 0.536 g of starting alcohol and 1.90 g (70%) of the title compound as a
bright yellow solid with mp 98-99.5 °C and MS(EI) 340 (M^+).

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Step 3:   N-(carbobenzyloxy)-4-[3-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-1-
azetidinyl]-3-fluoroaniline

A solution of 4-[3-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-1-azetidinyl]-3-
fluoronitrobenzene (1.70 g, 5.0 mmol) in 2:1 methanol/tetrahydrofuran (30 mL) was

5   degassed by repeated evacuation and filling with N_2 and then treated with 10%
palladium/carbon (0.170 g) under N_2. Solid ammonium formate was added, the
reaction mixture degassed a final time, and the mixture cooled with an ice bath due
to the observation of an exotherm. The color of the reaction mixture changed from
yellow to colorless. TLC analysis (2:1 hexane/ethyl acetate) revealed the reduction

10   to be complete. The reaction mixture was filtered through Celite® and the filtrate
concentrated *in vacuo* to give the intermediate aniline as a solid which was
immediately dissolved in 1:1 acetone/water, cooled to 0°C with an ice bath, and
treated with sodium bicarbonate (0.840 g, 10.0 mmol) and then benzyl chloroformate
(0.938 g, 0.785 mL, 5.5 mmol). The reaction mixture was left to stir overnight under

15   N_2 with gradual dissipation of the cooling bath. After a total of 16 h, the reaction
mixture was transferred to a separatory funnel along with dichloromethane (100
mL). After shaking, the organic phase was separated, washed with water, dried
over sodium sulfate, filtered and concentrated under reduced pressure to give a
crude oil. Chromatography over silica gel, eluting with 9:1 hexane/ethyl acetate,

20   afforded, after concentration of appropriate fractions, 1.68 g (76%) of the title
compound as a gum with MS(EI) 444 (M⁺).

Step 4:   (*R*)-[3-[4-[3-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-1-azetidinyl]-3-
fluorophenyl]-2-oxo-5-oxazolidinyl]methanol

A solution of N-(carbobenzyloxy)-4-[3-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-1-

25   azetidinyl]-3-fluoroaniline (1.60 g, 3.8 mmol) in dry tetrahydrofuran (20 mL) under
N_2 was cooled to -78 °C with a dry ice/acetone bath and treated with *n*-butyllithium
(2.40 mL of a 1.55 M solution in hexane, 3.8 mmol) via syringe. After 5 min at this
temperature, (*R*)-glycidyl butyrate (0.548 g, 0.538 mL, 3.8 mmol) was added. When
the addition was completed, the cooling bath was removed and the reaction mixture

30   allowed to warm to ambient temperature under N_2. After 2 h at this temperature,
TLC analysis (2:1 hexane/ethyl acetate) revealed the starting Cbz derivative was
consumed. The reaction mixture was concentrated *in vacuo* and the residue
dissolved in ethyl acetate, washed with water and brine, dried over sodium sulfate,
filtered and concentrated *in vacuo* to give a crude product. Chromatography over

35   silica gel, eluting with 30% ethyl acetate/dichlorom thane, afforded, after
concentration of appropriate fractions, 1.10 g (71%) of the title 5-(hydroxymethyl)-

oxazolidinone as a white solid with mp 143.5-144.5 °C and MS(EI) 410 (M⁺).

Step 5:   (R)-[[3-[4-[3-[(tert-butyldimethylsilyl)oxy]-3-methyl-1-azetidinyl]-3-
fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate

A solution of (R)-[3-[4-[3-[(tert-butyldimethylsilyl)oxy]-3-methyl-1-azetidinyl]-

5   3-fluorophenyl]-2-oxo-5-oxazolidinyl]methanol (1.00 g, 2.43 mmol) in dry

dichloromethane (15 mL) was cooled to 0 °C with an ice bath and treated with

triethylamine (0.295 g, 0.406 mL, 2.92 mmol) and then methanesulfonyl chloride

(0.321 g, 0.217 mL, 2.80 mmol) under N₂. After 2 h at 0°C, TLC analysis (5%

methanol/chloroform) revealed the reaction to be complete. The reaction mixture

10   was transferred to a separatory funnel along with more dichloromethane (75 mL).

The organic layer was washed with 0.5 N hydrochloric acid, saturated aqueous

sodium bicarbonate, water and brine, dried over sodium sulfate, filtered and

concentrated *in vacuo* to give 1.03 g (94%) of the title compound as a white solid

with mp 113-115 °C and MS(EI) 488 (M⁺).

15   **Step 6:**   (R)-[[3-[4-[3-[(tert-butyldimethylsilyl)oxy]-3-methyl-1-azetidinyl]-3-
fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]azide

A solution of (R)-[[3-[4-[3-[(tert-butyldimethylsilyl)oxy]-3-methyl-1-azetidinyl]-

3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]methanesulfonate (0.960 g, 2.10 mmol)

in dry N,N-dimethylformamide (20 mL) under N₂ was treated with sodium azide

20   (0.273 g, 4.2 mmol) at ambient temperature. The reaction mixture was heated to 70

°C for 3 h and then cooled to room temperature. TLC analysis (5%

methanol/chloroform) at this time revealed the reaction to be complete. The solvent

was removed *in vacuo* and the residue taken-up in dichloromethane (100 mL) and

water. The organic phase was separated, dried over sodium sulfate, filtered and

25   concentrated *in vacuo* to give 0.820 g (90%) of the title compound as a white solid

with mp 127-128 °C and MS(EI) 435 (M⁺).

Step 7:   (S)-N-[[3-[4-[3-[(tert-butyldimethylsilyl)oxy]-3-methyl-1-azetidinyl]-3-
fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of (R)-[[3-[4-[3-[(tert-butyldimethylsilyl)oxy]-3-methyl-1-azetidinyl]-

30   3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]azide (0.750 g, 1.72 mmol) in ethyl

acetate (20 mL) was degassed by repeated evacuation and filling with N₂. The

solution was then treated with 10% palladium/carbon (0.075 g) under a N₂ stream.

The atmosphere was replaced with H₂ (balloon) by repeated evacuation and filling

and the reaction mixture stirred at ambient temperature. TLC analysis (5%

35   methanol/chloroform) after 6 h revealed the reduction to be complete. The reaction

mixture was filtered through Celite® and the filtrate concentrated under reduced

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pressure. The residu was dissolved in dry dichloromethane (10 mL), cooled to 0 °C
with an ice bath, and treated with pyridine (0.680 g, 0.696 mL, 8.60 mmol) and
acetic anhydride (0.263 g, 0.243 mL, 2.58 mmol). The cooling bath was removed
and the reaction mixture stirred at ambient temperature under N_2. After 3 h the

5   reaction mixture was transferred to a separatory funnel along with dichloromethane
(100 mL). The mixture was washed with 10% hydrochloric acid, saturated aqueous
sodium bicarbonate and brine, dried over sodium sulfate, filtered and concentrated
in vacuo. Radial chromatography over silica gel, eluting with 3% and then 5%
methanol/chloroform, afforded, after concentration of appropriate fractions, 0.643 g

10 (83%) of the title compound as a white solid with mp 137-138 °C and MS(EI) 451
(M^+).

Step 8:   (S)-N-[[3-[3-fluoro-4-(3-hydroxy-3-methyl-1-azetidinyl)phenyl]-2-oxo-5-
             oxazolidinyl]methyl]acetamide

A solution of (S)-N-[[3-[4-[3-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-1-

15 azetidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.550 g, 1.22
mmol) in acetonitrile (20 mL) in a polypropylene bottle was treated with 40%
aqueous hydrofluoric acid (5 mL) at ambient temperature. After 16 h TLC analysis
(5% methanol/chloroform) revealed the deprotection was essentially complete. The
reaction mixture was transferred to an erlenmeyer flask along with some

20 dichloromethane (150 mL). The stirred mixture was carefully treated with
saturated aqueous sodium carbonate (300 mL, gas evolution). After gas evolution
ceased, the mixture was transferred to a separatory funnel and the phases
separated. The aqueous phase was neutralized to pH 7 by the addition of 6 N
hydrochloric acid and extracted with dichloromethane. The combined organic

25 extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. Radial
chromatography over silica gel, eluting with 5% methanol/chloroform, afforded, after
concentration of appropriate fractions, 0.374 g (91%) of the title oxazolidinone
antibacterial agent as a white solid with mp 152-153 °C and MS(EI) 337 (M^+).

30 Pyrrolidinone-Phenyloxazolidinone Examples
EXAMPLE 8:   (S)-N-[[3-[4-(1-Aza-5,5-dimethyl-4,6-dioxabicyclo[3.3.0]octan-1-yl)-3-
fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:
          3-Fluoro-1-nitro-4-(2,5-dihydropyrryl)benzene:
A solution of 2.30g(14.47mmol) of 2, 4-dinitrofluorobenzene and

35 5.04g(28.93mmol) of dibasic potassium phosphate in 30mL DMSO was treated with
1.0g(14.47mmol) of 3-pyrroline, followed by warming at 60°C for 24h. The solution

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was cooled and diluted with 100mL chloroform followed by extraction with water (5 x 75mL). Drying (Na$_2$SO$_4$) and concentration *in vacuo* afforded a yellow solid which was recrystallized from hot ethyl acetate-hexane to afford 2.58g(86%) of the title compound as yellow prisms, mp 132-134°C.

5   3-Fluoro-1-nitro-4-(*cis*-3,4-dihydroxypyrrolidinyl)-benzene:

A solution of 1.25g(6.02mmol) of the previous compound and 881mg(7.52mmol) of N-methylmorpholine N-oxide in 60mL acetone and 13mL water was treated with 4mL of a 2.5% osmium tetroxide solution in *tert*-butyl alcohol followed by stirring at ambient temperature for 24h. The solution with 500mg of

10   sodium bisulfite, 2g of magnesol, and 10mL water followed by stirring for 20min. The mixture was filtered through celite, washing the filter cake with acetone. The filtrate was concentrated *in vacuo* and diluted with 100mL ethyl acetate and 150mL water. The aqueous layer was extracted with ethyl acetate (3 x 100mL) and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated *in vacuo* to afford a

15   yellow solid. This material was recrystallized from hot acetone-hexane to afford 1.33g(91%) of the title compound as a yellow solid, mp 151-153°C.

          1-(1-aza-5,5-dimethyl-4,6-dioxabicyclo[3.3.0]octan-1-yl)-2-fluoro-4-nitrobenzene (3):

A solution of 1.27g(5.24mmol) of the previous diol in 10mL

20   dimethylformamide was treated with 1.09g(1.3mL, 10.49mmol) of 2,2-dimethoxypropane and a few crystals of *p*-toluenesulfonic acid, followed by stirring at ambient temperature for 24h. The solution was diluted with 50mL chloroform and extracted with water (5 x 30mL). Drying (Na$_2$SO$_4$) and concentration *in vacuo* afforded 1.45g(98%) of the title compound as a yellow solid, sufficiently pure for

25   further use. An analytical sample was obtained by recrystallization from hot acetone-hexane, mp 113-114°C.

          1-(1-aza-5,5-dimethyl-4,6-dioxabicyclo[3.3.0]octan-1-yl)-2-fluoro-4-(phenylmethoxycarbonyl)aminobenzene:

A solution of 1.45g(5.14mmol) of the previous compound in 50mL

30   tetrahydrofuran was treated with 260mg of 10% palladium on carbon followed by hydrogenation at one atmosphere for 3h. The reaction vessel was purged with nitrogen and treated with 20mL saturated sodium bicarbonate solution followed by cooling to 0°C and addition of 1.75g(1.47mL, 10.27mmol) f benzyl chloroformate. The solution was stirred at 0°C for 30min followed by warming to ambient

35   temperature for 18h. The mixture was diluted with 50mL ethyl acetate and 50mL water and filtered through celite, washing the filter

cake with thyl acetate. Th filtrate layers were separated and the organic phase
was extracted with 50mL water and 50mL saturated sodium chlorid solution.
Drying (Na$_2$SO$_4$) and concentration *in vacuo* afforded a light purple solid which was
recrystallized from hot ethyl acetate-hexane to afford 1.56g(79%) of the title

5   compound as fine white crystals. ^{1}H NMR(CDCl$_3$): δ7.39, 7.25, 6.93, 6.67, 5.19,
4.80, 3.73, 2.97, 1.53, 1.37.

(R)-[3-[4-(1-Aza-5,5-dimethyl-4,6-dioxabicyclo[3.3.0]octan-1-yl)-3-fluorophenyl]-
2-oxo-5-oxazolidinyl]methanol (5):

A solution of 1.36g(3.52mmol) of Cbz derivative of the previous compound in

10   48mL tetrahydrofuran at -78°C was treated dropwise with 2.41mL(1.6M, 3.87mmol)
of n-butyllithium in hexane, follwed by stirring at -78°C for 30min. The solution
was then treated with 558mg(0.55mL, 3.87mmol) of neat (R)-(+)-glycidiyl butyrate,
followed by warming to 0°C for 30min and then to ambient temperature for 18h.
The solution was then cooled to 0°C and treated with 4mL saturated aqueous

15   ammmonium chloride solution, followed by dilution with 200mL dichloromethane
and extraction with water (2 x 50mL) and saturated ammonium chloride solution
(50mL). Drying (Na$_2$SO$_4$) and concentration *in vacuo* afforded a brown solid which
was chromatographed over 80g of 230-400 mesh silica gel, eluting with 2%(v/v)
methanol in dichloromethane. These procedures afforded 840mg of the title

20   compound as and off-white solid. ^{1}H NMR(CDCl$_3$): δ7.34, 7.06, 6.71, 4.80, 4.75,
4.01, 3.73, 3.67, 3.56, 2.95, 1.50, 1.36.   (S)-[[3-[4-(1-Aza-5,5-dimethyl-4,6-
dioxabicyclo[3.3.0]octan-1-yl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]
methanesulfonate:

A solution of 791mg(2.25mmol) of the previous alcohol and 283mg(0.39mL,

25   2.81mmol) of triethylamine in 11mL dichloromethane at 0°C was treated with
296mg(0.20mL, 2.58mmol) of methanesulfonyl chloride, followed by stirring at 0°C
for 30min. The mixture was warmed to ambient temperature and diluted with 75ml
dichloromethane followed by extraction with water (2 x 30mL) and with saturated
sodium bicarbonate solution (30mL). Drying(Na$_2$SO$_4$) and concentration *in vacuo*

30   afforded 810mg(84%) of the title mesylate as an off-white solid sufficiently pure for
further use. ^{1}H NMR(CDCl$_3$): δ7.36, 7.07, 6.73, 4.90, 4.82, 4.48, 4.41, 4.10, 3.89,
3.77, 3.10, 3.02, 1.51, 1.37.

(S)-N-[[3-[4-(1-Aza-5,5-dimethyl-4,6-dioxabicyclo[3.3.0]octan-1-yl)-3-
fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

35   A solution of 810mg (1.88mmol) of the previous mesylate in 8mL of 1:1

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tetrahydrofuran-isopropyl alcohol in a resealable thick wall tube was treated with
8mL of ammonium hydroxide. The tube was sealed and warmed at 100°C for 22h.
The tube was cooled and the reaction mixture was partitioned between chloroform
and water. The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to
5   afford 520mg of a tan solid, which was used dissolved in 2mL pyridine and treated
with 357mg(0.33mL, 3.50mmol) acetic anhydride followed by stirring at ambient
temperature for 18h. The solution was diluted with chloroform (20mL) and
extracted with water (4 x 20mL). The organic layer was dried (Na₂SO₄) and
concentrated *in vacuo* and the solid obtained recrystallized from chloroform-hexane
10   to afford 350mg(59%) of the title acetamide as off-white needles, mp 195-7°C.

EXAMPLE 9:   (S)-N-[[3-[4-(3,4-*cis*-dihydroxypyrrolidinyl)-3-fluorophenyl]-2-oxo-5-
oxazolidinyl]methyl]acetamide (9):

A solution of 249mg(0.63mmol) of the compound prepared in Example 8 in
15   2mL tetrahydrofuran was treated with 2mL 2*N* hydrochloric acid solution, followed
by stirring at ambient temperature for 18h. The mixture was concentrated *in vacuo*
and the residue treated with 30mL saturated sodium bicarbonate solution. The
mixture was extracted with ethyl acetate (2 x 50mL), dried (Na₂SO₄) and
concentrated *in vacuo* to afford 110mg of an off-white solid.
20   This material was subjected to radial chromatography on a 2mm
chromatotron plate eluting with 7%(v/v) methanol in dichloromethane. These
procedures afforded 60mg(28%) of the title diol as a white solid, mp 183-
189°C(decomposition).

25   EXAMPLE 10: (S)-N-[[3-[4-(3-hydroxypyrrolidinyl)-3-fluorophenyl]-2-oxo-5-
oxazolidinyl]methyl]acetamide:
3-Fluoro-4-(3-hydroxypyrrolidinyl)nitrobenzene:

To a solution of 3-pyrrolidinol (1.82 g) and 3,4-difluoronitrobenzene (3.0 g) in
dimethylformamide (30 ml) was added potassium carbonate (3.94 g). The mixture
30   was stirred at room temperature overnight and then filtered followed by washing
with dichloromethane. The filtrate combined was concentrated under reduced
pressure. The residue obtained was chromatographed over a silica gel column
eluting with ethyl acetate/hexane with increasing in the content of ethyl acetate
(50% to 60%). The appropriate fractions were pooled and concentrated under reduced
35   pressure to give the title compound (4.83 g); ¹H NMR (CD₃OD, 270 MHz), δ 0.85
(2H, m), 2.25-2.57 (4H, m), 3.26 (1H, m), 5.47 (1H, t, J=8.6 Hz), 6.62 (1H, dd, J=2.4,

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14.0 Hz), 6.69 (1H, dd, J=2.4, 8.6 Hz).

3-Fluoro-4-[3-(tert-butyldimethylsilyloxy)pyrrolidinyl]nitrobenzene:

A mixture of the previous compound (4.83 g), triethylamine (9.5 ml) and
5   dimethylaminopyridine (2.79 g) in tetrahydrofuran (100 ml) was treated with tert.-
butyldimethylsilyl chloride (5.15 g) at 0°C. and stirred at room temp. for 2 days. The
mixture was filtered and the insoluble material was washed with dichloromethane.
The filtrate combined was washed with brine, dried over sodium sulfate and
concentrated under reduced pressure. The residue obtained was chromatographed
10   over a silica gel column eluting with ethylacetate/hexane (70/30). The appropriate
fractions were combined and concentrated under reduced pressure to give the title
compound (11) (6.45 g); ^{1}H NMR (CDCl$_3$), δ 0.09 (6H, s), 0.88 (9H, s), 2.02 (2H, m),
3.42-3.78 (4H, m), 4.52 (1H, m), 6.53 (1H, t, J=8.9 Hz), 7.87 (1H, dd, J=2.4, 14.0 Hz),
7.94 (1H, dd, J=2.4, 8.9 Hz).

15   ### 3-Fluoro-4-[3-(tert-butyldimethylsilyloxy)pyrrolidinyl]aniline:

Palladium on carbon (10%, 500 mg) was added to a mixture of the previous
compound (5.0 g) in a mixed solvent of dichloromethane (20 ml) and methanol (100
ml). The mixture was stirred under 1 atmosphere of hydrogen for 6 h, then filtered
and the palladium on carbon was washed with methanol and dichloromethane. The
20   combined filtrates were concentrated under reduced pressure to give the title
compound (4.52 g); ^{1}H NMR (CDCl$_3$), δ 0.08 (6H, s), 0.88 (9H, s), 1.87 (1H, m), 2.11
(1H, m), 3.05 (1H, m), 3.29 (2H, m), 3.56 (1H, m), 4.48 (1H, m), 6.38 (1H, dd, J=2.4,
8.9 Hz), 6.44 (1H, dd, J=2.4, 14.0 Hz), 6.61 (1H, t, J=8.9 Hz).

1-Benzyloxycarbonylamino-4-[3-(tert-butyldimethylsilyloxy)pyrrolidinyl]-3-
25   fluorobenzene:

Benzyl chloroformate (3.0 ml) was added to a mixture of the previous
compound (4.52 g) and sodium bicarbonate (1.76 g) in tetrahydrofuran (50 ml) at
0°C. The mixture was stirred at room temperature overnight and then filtered
followed by washing with tetrahydrofuran. The combined filtrates were dried over
30   sodium sulfate and concentrated under reduced pressure. The residue obtained was
subjected to a silica gel column eluting with hexane/ethyl acetate (90/10). The
appropriate fractions was unifi d and concentrated under reduced pressure to give
the title compound (4.40 g); ^{1}H NMR (CDCl$_3$), δ 0.08 (6H, s), 0.88 (9H, s), 1.87 (1H,
m), 2.11 (1H, m), 3.05 (1H, m), 3.29 (2H, m), 3.56 (1H, m), 4.48 (1H, m), 5.18 (2H, s),
35   6.59 (1H, t, J=8.9 Hz), 6.88 (1H, dd, J=2.4, 8.9 Hz), 7.10 (1H, dd, J=2.4, 14.0 Hz),
7.36 (5H, m).

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<u>(S)-[[3-[4-[3-(*tert*-butyldimethylsilyloxy)pyrroldinyl]-3-fluorophenyl]]-2-oxo-5-oxazolidinyl]methanol:</u>

A solution of the previous compound (4.40 g) in dry tetrahydrofuran (50 ml) was cooled to -78°C under nitrogen and treated with 7.3 ml (1.6 M in hexane) of n-

5   BuLi with stirring for 5 min. The mixture was treated with 1.65 ml of (R)-(+)-glycidyl butyrate and was allowed to warm slowly to room temperature overnight. The reaction was quenched by addition of saturated ammonium sulfate solution (10 ml) and the mixture extracted with dichloromethane (3 x 50 ml). The organic layer combined was washed with brine, dried over sodium sulfate and concentrated under

10   reduced pressure. The residue obtained was chromatographed over a silica gel column eluting with hexane/ethyl acetate with increasing in the content of ethyl acetate (50% to 70%). The appropriate fractions were pooled and concentrated under reduced pressure to give the title compound (1.44 g); ^{1}H NMR (CDCl$_3$), δ 0.08 (6H, s), 0.88 (9H, s), 1.91-2.10 (2H, m), 3.18 (1H, m), 3.39-3.48 (2H, m), 3.63 (1H, m), 3.78

15   (1H, m), 3.87-4.01 (3H, m), 4.48 (1H, m), 4.66 (1H, m), 6.63 (1H, t, J=9.5 Hz), 7.04 (1H, dd, J=2.4, 9.5 Hz), 7.32 (1H, dd, J=2.4, 14.6 Hz).

<u>(S)-[[3-[4-[3-(*tert*-butyldimethylsilyloxy)pyrrolidinyl]-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl] methanesulfonate:</u>

To a solution of the previous compound (1.44 g) in pyridine (10 ml) was added

20   p-toluene sulfonylchloride (0.88 g) at 0°C with stirring. The mixture was stirred at room temp. for over night. Water (40 ml) was added slowly to the mixture with stirring and the mixture was futher stirred for 1 hr to give crystals. The crystals were collected by filtration, washed with water and dried at 40 °C under reduced pressure overnight to give the title compound (1.96 g); ^{1}H NMR (CDCl$_3$), δ 0.09 (6H,

25   s), 0.88 (9H, s), 1.90-2.08 (2H, m), 2.46 (3H, s), 3.21 (1H, m), 3.40-3.49 (2H, m), 3.65 (1H, m), 3.81 (1H, dd, J=5.9, 8.9 Hz), 4.03 (1H, t, J=8.9 Hz), 4.24 (2H, m), 4.49 (1H, m), 4.80 (1H, m), 6.63 (1H, t, J=9.5 Hz), 6.96 (1H, dd, J=2.4, 9.5 Hz), 7.23 (1H, dd, J=2.4, 14.6 Hz), 7.36 (2H, d, J=7.8 Hz), 7.79 (2H, d, J=7.8 Hz).

<u>(S)-N-[[3-[4-[3-(*tert*-butyldimethylsilyloxy)pyrrolidinyl]-3-fluorophenyl]-2-oxo-5-</u>

30   <u>oxazolidinyl]methyl]acetamide:</u>

A mixture of the previous compound (1.96 g) in dimethylformamide (20 ml) was tr ated with sodium azide (455 mg) and warmed at 60°C for over night. After cooling to room temperature, the mixture was filtered and the precipitate was washed with dichloromethane. The combined filtrates were concentrated under

35   reduced pressure. The residue obtained was chromatographed over a silica gel column eluting with hexane/acetone (80/20). The appropriate fractions were

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combined and concentrated under reduced pressure to give a compound (1.40 g). A solution f this compound in dry tetrahydrofuran (20 ml) was treated with triphenylphosphine (868 mg) and stirred at room temp. for 2 hr. The mixtrure was treated with water (0.5 ml) and stirred at 40 °C for 4 hr, then at room temperature

5   overnight. The mixture was concentrated under reduced pressure and dried by azeotropic evaporation with toluene. The residue obtained was suspended in dichloromethane (20 ml) and treated with pyridine (0.5 ml) and acetic anhydride (0.6 ml) at 0°C. The mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was subjected to a silica gel

10   column eluting with methanol/dichloromethane with increasing in the content of methanol (1% to 3%). The appropriate fractions were pooled and concentrated under reduced pressure to give the title compound (1.502 g); ^{1}H NMR (CDCl$_3$), δ 0.08 (6H, s), 0.88 (9H, s), 1.89-2.09 (2H, m), 2.02 (3H, s), 3.18 (1H, m), 3.36-3.67 (6H, m), 3.71 (1H, dd, J=6.8, 8.9 Hz), 3.99 (1H, t, J=8.9 Hz), 4.48 (1H, m), 4.76 (1H, m), 6.20 (1H,

15   broad, NH), 6.61 (1H, t, J=9.2 Hz), 6.98 (1H, dd, J=2.4, 9.2 Hz), 7.30 (1H, dd, J=2.4, 15.1 Hz).

(S)-N-[[3-[4-(3-hydroxypyrrolidinyl)-3-fluorophenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

A mixture of the previous compound (1.50 g) in dry tetrahydrofuran (8 ml)

20   was treated with tetrabutylammonium fluoride (6.7 ml; 1.0 M in tetrahydrofuran) at 0 °C and allowed to warm to room temp. with stirring for 4 hr. The mixture was treated with water (50 ml) and extracted with dichloromethane (30 ml x 4). The organic layer unified was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to a silica gel

25   column eluting with acetone/hexane (80/20). The appropriate fractions were combined and concentrated under reduced pressure to give the title compound (0.77 g); ^{1}H NMR (DMSO-d$_6$), δ 1.78-2.00 (2H, m), 1.80 (3H, s), 3.12 (1H, m), 3.26-3.54 (5H, m), 3.67 (1H, dd, J=6.8, 8.9 Hz), 4.04 (1H, t, J=8.9 Hz), 4.34 (1H, m), 4.68 (1H, m), 4.91 (1H, d, J=4.1 Hz, OH), 6.72 (1H, t, J=9.7 Hz), 7.07 (1H, dd, J=2.4, 9.7 Hz),

30   7.38 (1H, dd, J=2.4, 16.2 Hz), 8.23 (1H, t, J=5.7 Hz, NH).

EXAMPLE 11:   (S)-N-((3-(3-fluoro-4-(3-oxopyrrolidinyl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide:

7-Benzyl-7-aza-1,4-dioxaspiro(4,5)nonane:

35   To a susp nsion of 1-N-benzyl-3-pyrrolidinon (1.92 g) and ethylene glycol (6.81 g) in benzene (70 ml) was added p-toluene sulfonic acid monohydrate (1.93 g).

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The mixture was refluxed with azeotropic removal of water by means of a D an-Stark trap for 6 hr. After cooling to room temp., the mixture was washed with sat. sodium bicarbonate aq. (50 mlx3). The water layer was then extracted with dichloromethane (30 mlx3). The organic layers were unified, washed with brine,

5   dried over sodium sulfate and concentrated under reduced pressure to give the title compound (1.57 g); ^{1}H NMR (CDCl$_3$), δ 2.06 (2H, t, J=7.3 Hz), 2.64 (2H, s), 2.66 (2H, t, J=7.3 Hz), 3.61 (2H, s), 3.89 (4H, m), 7.28 (5H, m).

    7-Aza-1,4-dioxaspiro(4.5)nonane:

    Palladium hydroxide on carbon (20%, 200 mg) was added to a solution of the

10   previous compound (1.57 g) in a mixed solvent of dichloromethane (10 ml) and methanol (20 ml). The mixture was stirred under 3kgf/cm^2 of hydrogen for 2 days, then filtered and the palladium hydroxide on carbon was washed with methanol and dichloromethane. The filtrate combined was concentrated under reduced pressure to give the title compound (1.38 g); ^{1}H NMR (CDCl$_3$), δ 2.17 (2H, t, J=7.3 Hz), 3.35

15   (2H, s), 3.52 (2H, t, J=7.3 Hz), 3.99 (4H, s).

    4-(7-Aza-1,4-dioxaspiro(4.5)nonan-7-yl)-3-fluoronitrobenzene:

    Following the general procedure of Example 9 and making non-critical variations but starting with the previous compound (1.38 g), the title compound (1.50 g) was obtained, ^{1}H NMR (CDCl$_3$), δ 2.18 (2H, t, J=7.3 Hz), 3.67 (2H, s), 3.72

20   (2H, t, J=7.3 Hz), 4.02 (4H, s), 6.53 (1H, t, J=7.3 Hz), 7.88 (1H, dd, J=2.4, 14.0 Hz), 7.94 (1H, dd, J=2.4, 8.9 Hz).

    4-(7-aza-1,4-dioxaspiro(4.5)nonan-7-yl)-3-fluoro-1-(phenylmethoxycarbonylamino)-benzene:

    Following the general procedure of example 9 and making non-critical

25   variations but starting with the previous compound (1.49 g), the title compound (2.44 g) was obtained, ^{1}H NMR (CDCl$_3$), δ 2.16 (2H, t, J=6.8 Hz), 3.41 (2H, t, J=6.8 Hz), 3.46 (2H, s), 3.98 (4H, s), 5.18 (2H, s), 6.60 (1H, t, J=9.2 Hz), 6.91 (1H, dd, J=2.4, 9.2 Hz), 7.22 (1H, dd, J=2.4, 14.0 Hz), 7.37 (5H, m).

    (R)-(3-(3-fluoro-4-(7-aza-1,4-dioxaspiro(4.5)nonan-7-yl)phenyl)-2-oxo-5-

30   oxazolidinyl)methanol:

    A solution of the previous compound (2.44 g) in dry dimethylformamide (25 ml) was cooled to -78 °C under nitrogen and treated with 6.6 ml (1.0 M in tetrahydrofuran) of lithium bis(trimethylsilyl)amide with stirring for 5 min. The mixture was treated with 0.93 ml of (R)-(-)-glycidyl butyrate and was allowed to

35   warm slowly to room temp. for over night. Small excess of lithium bis(trimethylsilyl)amide was quenched by addition of water (5 ml). The mixture was

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concentrated under reduced pressure and dried by azeotropic evaporation with toluen . The residue was suspended in dichloromethan (100 ml) and the insoluble materaial was removed by filtration. The filtrate was concentrated under reduced pressure and the residue obtained was then subjected to a silica gel column eluting

5   with hexane/acetone (50/50). The appropriate fractions were pooled and concentrated under reduced pressure to give the title compound (1.79 g); ^{1}H NMR (DMSO-d_6), δ 2.07 (2H, t, J=7.3 Hz), 3.35 (4H, overlapped with signals due to the solvent), 3.50-3.69 (2H, m), 3.78 (1H, dd, J=7.3, 9.2 Hz), 3.92 (4H, s), 4.02 (1H, t, J=9.2 Hz), 4.67 (1H, m), 5.20 (1H, t, J=5.9 Hz, OH), 6.77 (1H, t, J=10.3 Hz), 7.13 (1H, dd, J=2.4, 10.3

10 Hz), 7.46 (1H, dd, J=2.4, 16.2 Hz).

(R)-N-((3-(3-fluoro-4-(7-aza-1,4-dioxaspiro(4.5)nonan-7-yl)phenyl)-2-oxo-5-oxazolidinyl)methyl)azide:

Following the general procedure of Example 9 and making non-critical variations but starting with the previous compound (1.78 g), the title compound

15 (1.76 g) was obtained, ^{1}H NMR (CDCl$_3$), δ 2.14 (2H, t, J=7.3 Hz), 2.44 (3H, s), 3.45 (2H, t, J=7.3 Hz), 3.49 (2H, s), 3.73-4.13 (2H, m), 3.98 (4H, s), 4.24 (2H, m), 4.80 (1H, m), 6.60 (1H, t, J=9.5 Hz), 6.96 (1H, dd, J=2.4, 9.5 Hz), 7.23 (1H, dd, 2.4, 14.6 Hz), 7.36 (2H, d, J=7.8 Hz), 7.78 (2H, d, J=7.8 Hz).

(R)-N-((3-(3-fluoro-4-(7-aza-1,4-dioxaspiro(4.5)nonan-7-yl)phenyl)-2-oxo-5-

20 oxazolidinyl)methyl)acetamide:

Following the general procedure of Example 9 and making non-critical variations, Lindlar catalyst (150 mg) was then added to a mixture of the previous compound (17) (1.45 g) in a mixed solvent of dichloromethane (10 ml) and methanol (40 ml). The mixture was stirred under an atmospheric press. of hydrogen for 2

25 days, then filtered and the catalyst was washed with methanol and dichloromethane. The filtrate combined was concentrated under reduced pressure. The residue obtanied was suspended in dichloromethane (20 ml) and treated with pyridine (0.3 ml) and acetic anhydride (0.7 ml) at 0 °C. The mixture was stirred at room temp. for over night and concentrated under reduced pressure. The residue

30 was subjected to a silica gel column eluting with methanol/dichloromethane with incresing in the content of methanol (2% to 5%). The appropriate fractions were pooled and concentrated under reduced pressure to give the title compound (0.72 g); ^{1}H NMR (CDCl$_3$), δ 2.01 (3H, s), 2.16 (2H, t, J=7.3 Hz), 3.43 (2H, t, J=7.3 Hz), 3.47 (2H, s),

35

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3.53-3.67 (2H, m), 3.71 (1H, dd, J=6.8, 9.2 Hz), 3.98 (5H, m), 4.75 (1H, m), 6.27 (1H, broad), 6.61 (1H, t, J=9.2 Hz), 6.99 (1H, dd, J=2.4, 9.2 Hz), 7.33 (1H, dd, J=2.4, 15.1 Hz).

(S)-N-((3-(3-fluoro-4-(3-oxopyrrolidinyl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide:

A mixture of the previous compound (610 mg) in acetone (12 ml) and water (3.7 ml) was treated with p-toluene sulfonic acid monohydrate (609 mg) and refluxed for 3 hours. After cooling to room temp., the mixture was concentrated under reduced pressure. The residue was treated with 5 ml of triethylamine and extracted with dichloromethane (30 mlx5). The organic layers were combined, washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue obtained was subjected to a silica gel column eluting with hexane/acetone (50/50). The appropriate fractions were combined and concentrated under reduced pressure to give the title compound (390 mg); ^{1}H NMR (CDCl$_3$), δ 2.03 (3H, s), 2.65 (2H, t, J=6.8 Hz), 3.47-3.78 (7H, m), 4.02 (1H, t, J=8.9 Hz), 4.76 (1H, m), 6.18 (1H, t, J=5.9 Hz, NH), 6.77 (1H, t, J=9.2 Hz), 7.09 (1H, dd, J=2.4, 9.2 Hz), 7.43 (1H, dd, J=2.4, 15.1 Hz).

EXAMPLE 12:   (S)-N-((3-(3-Fluoro-4-(3-(phenylmethoxyacetylamino)-pyrrolidinyl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide

Step 1:   3-Fluoro-1-nitro-4-(3-trifluoroacetylamino)pyrrolidinylbenzene

A solution of 4.49g(20.54mmol) of 3-(trifluoroacetylamino)pyrrolidine hydrochloride and 2.97g(18.68mmol) of 3,4-difluoronitrobenzene and 7.16g(41.10mmol) of dibasic potassium phosphate in 87mL DMSO was warmed at 90°C for 18h. The mixture was cooled and diluted with 300mL of ethyl acetate. The solution was extracted with water (5 x 100mL) and dried (Na$_2$SO$_4$). Concentration *in vacuo* afforded a yellow solid which was recrystallized from hot ethyl acetate-hexane to afford 5.0g(84%) of the title product as a yellow crystalline solid, mp 165-167°C.

Step 2:   3-Fluoro-1-(phenylmethoxycarbonyl)amino-4-(3-trifluoroacetylamino)pyrrolidinylbenzene

A solution of 4.10g(12.76mmol) of the nitro compound in 100mL ethyl acetate was treated with 500mg of 10% palladium on carbon, followed by hydrogenation at atmospheric pressure for 4hours. The mixture was filtered through celite washing the filter cake with ethyl acetate. The filtrate was concentrated *in vacuo* and the residue was dissolved in 50mL acetone and treated with 75mL saturated NaHCO$_3$

solution followed by cooling to 0°C and treatm nt with 4.36g(3.64mL, 25.53mmol) of

benzyl chloroformate. The solution was then warmed to ambient temperature for

18h. The mixture was diluted with 200ml ethyl acetate and was extracted with

water (2 x 50mL) followed by drying (Na$_2$SO$_4$). Concentration *in vacuo* afforded a

5   beige solid which was recrystallized from hot ethyl acetate-hexane to afford

4.41g(81%) of the title cbz derivative as faint beige needles, mp 143-145°C.

Step 3:   3-Fluoro-1-(phenylmethoxycarbonyl)amino-4-(3-(1,3-dimethylexahydro-
2-oxo-1,35-triazin-5-yl)pyrrolidinyl)benzene

A solution of 1.86g(4.37mmol) of the Cbz derivative in 36mL THF was treated

10   with 50mL of 2*N* NaOH solution followed by warming at reflux for 36h. The

solution was cooled and diluted with 50mL water followed by extraction with ethyl

acetate (4 x 75mL). The combined organic layers were extracted with saturated

NaCl solution followed by drying (Na$_2$SO$_4$) and concentration *in vacuo*. The amber

oil obtained was dissolved in 20mL dioxane and 40mL toluene and the resulting

15   solution treated with 385mg(4.37mmol) of N, N'-dimethylurea and 5mL of 37%

aqueous formaldehyde solution. The mixture was warmed at reflux until *ca.* 5ml

water had collected in a Dean-Stark trap. The solution was cooled and concentrated

in vacuo. The residue was chromatographed over 180g of 230-400 mesh silica gel,

eluting with 2%(v/v) methanol in dichloromethane. These procedures afforded

20   1.40g(73%) of the title product as fine white crystals, mp 192-194°C.

Step 4:   (R)-(3-(3-Fluoro-4-(3-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazin-5-
yl)pyrrolidnyl)phenyl)-2-oxo-5-oxazolidinyl)methanol

A solution of 737mg(1.67mmol) of the triazone in 10mL DMF at -50°C was

treated with 1.84mL(1.84mmol) of lithium hexamethyldisilazide in THF. The

25   solution was stirred at -50°C for 5min, followed by addition of 265mg(0.26mL,

1.84mmol) of (R)-(+)-glycidiyl butyrate. The solution was then warmed to ambient

temperature for 18h. The mixture was concentrated *in vacuo* (*ca.* 0. 3mmHg) and

the residue was chromatographed over 36g of 230-400mesh silica gel, eluting with

3%(v/v) methanol in dichloromethane. These procedures afforded 400mg(59%) of the

30   title product as a white solid. ^{1}H NMR(CDCl$_3$): δ7.36, 7.05, 6.65, 4.72, 4.27, 4.18,

3.95, 3.77, 3.46, 2.88, 2.17, 1.94.

St p 5:   (R)-(3-(3-Fluoro-4-(3-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazin-5-
yl)pyrrolidnyl)phenyl)-2-oxo-5-oxazolidinyl)methanesulfonate

A solution of 395mg(0.97mmol) of the oxazolidinone, and 146mg(0.20mL,

35   1.45mmol) of triethylamine in 5mL dichloromethane at 0°C was treated with

471mg(0.32mL) of methanesulfonyl chloride. The solution was stirred at 0°C for 30

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minutes, followed by warming to ambient temperature. The solution was treated
with water and the aqueous lay r extracted with dichloromethane. The combined
organic layers were dried (Na$_2$SO$_4$) and concentrated *in vacuo* to afford 460mg(98%)
of the title product as an off-white solid suitable for use in the next step. ^{1}H

5   NMR(CDCl$_3$): δ7.33, 7.03, 6.63, 4.89, 4.45, 4.27, 4.18, 4.12, 3.89, 3.76, 3.55, 3.47,
3.38, 3.10, 2.88, 2.16, 2.08, 1.92.

Step 6:   (S)-N-((3-(3-Fluoro-4-(3-(phenylmethoxyacetylamino)-
pyrrolidinyl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide

A solution of 460mg(0.97mmol) of the mesylate in 15mL of isopropyl alcohol

10 and 15mL ammonium hydroxide in a sealed tube was warmed at 100°C for 18hours.
The mixture was cooled and diluted with water followed by extraction with
chloroform. The organic layer was dried (Na$_2$SO$_4$) and concentrated *in vacuo*. The
residue was dissolved in 4mL pyridine and treated with 0.5ml acetic anhydride
followed by stirring at ambient temperature for 18hours. The mixture was

15 concentrated *in vacuo* to afford an oil which was dissolved in chloroform and
extracted with water. The organic layer was dried (Na$_2$SO$_4$) and concentrated *in
vacuo* to afford 472mg of the acetamide derivative, which was directly dissolved in
4mL of 1N HCL solution followed by stirring at ambient temperature for 18hours.
The mixture was concentrated *in vacuo* and dissolved in 4mL acetone and treated

20 with 2mL of saturated NaHCO$_3$ solution followed by treatment with 217mg(0.14mL,
1.18mmol) of benzyloxyacetyl chloride, followed by stirring at ambient temperature
for 1h. The mixture was concentrated *in vacuo* and the residue was
chromatographed over 25g of 230-400 mesh silica gel, eluting with 2%(v/v) methanol
in dichloromethane and then with 3%(v/v) methanol in dichloromethane. These

25 procedures afforded 189mg(40%) of the benzyloxyacetamide derivative product as a
white solid. ^{1}H NMR(CDCl$_3$): δ7.33, 7.02, 6.81, 6.68, 6.08, 4.75, 4.60, 4.01, 3.71,
3.61, 3.34, 2.32, 2.02, 1.91.

EXAMPLE 13:   (S)-N-((3-(3-Fluoro-4-(3-(hydroxyacetylamino)pyrrolidinyl)phenyl)-2-

30 oxo-5-oxazolidinyl)methyl)acetamide

Continuing from the procedure of Example 12, Step 6, a solution of
189mg(0.39mmol) of the benzyloxyacetamide in 5mL methanol and 5mL THF was
treated with 200mg of 10% palladium on carbon followed by hydrogenation at
atmospheric pressure for 1h. The solution was diluted with methanol and filtered

35 through celite, washing the filter cake with methanol. The filtrate was concentrated
in vacuo to afford an oil, which was chromatographed over 10g of 230-400 mesh

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silica gel, eluting with 7%(v/v) methanol in dichloromethan . These procedures
afforded 95mg(62%) of the hydroxyacetamide d rivativ product as a pink solid. ^{1}H
NMR(CDCl$_3$): δ7.41, 7.10, 6.78, 4.77, 4.53, 4.10, 4.00, 3.77, 3.57, 3.32, 2.30, 1.99,
1.98.

5

EXAMPLE 14:   (S)-N-[[3-Fluoro-4-(cis-3-(methoxycarbonylamino)-4-
methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

Step 1:   cis-3-(1,1-dimethylethoxycarbonylamino)-4-methylpyrrolidine

A solution of 1.5g(5.2mmol) of cis-1-phenylmethyl-3-(1,1-
10   dimethylethoxycarbonylamino)-4-methylpyrrolidine (cf. US 4,753,953) in 50mL
methanol was treated with 200mg of Pd(OH)$_2$/C followed by hydrogenation under 1
atmosphere of H$_2$ for 3.5h. The mixture was filtered through celite, washing the
filter cake with methanol. The filtrate was concentrated in vacuo to afford a
colorless oil, which was used directly in the next step. ^{1}H NMR (CD$_3$OD) δ 4.85,
15   4.03, 3.14, 3.05, 2.66, 2.45, 2.23, 1.46, 0.95.

Step 2:   3-Fluoro-1-nitro-4-[cis-3-(1,1-dimethylethoxycarbonylamino)-4-
methylpyrrolidinyl]benzene

A solution of the previously obtained compound and 1.8g(10.3mmol) of
dibasic potassium phosphate in 40mL DMSO was warmed at 90°C for 18h. The
20   mixture was cooled and diluted with 125mL ethyl acetate, followed by extraction
with water (4 x 75mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated in
vacuo to afford 1.75g of a yellow solid, sufficiently pure for further use. MS (EI)
m/z 339 (M+), 339, 282, 266,
223, 222, 208, 207, 154, 70, 57.

25   **Step 3:**   3-Fluoro-1-nitro-[cis-3-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazin-5-yl)-
4-methylpyrrolidinyl]benzene

A solution of 1.75g(5.17mmol) of the previous compound in 50mL
trifluoroacetic acid was stirred at ambient temperature for 18h. The solution was
concentrated in vacuo and the red-brown oil obtained was dissolved in ethyl acetate
30   and extracted cautiously with saturated NaHCO$_3$ solution (4 x). The combined
aqueous layers were extracted with ethyl acetate, and the combined organic layers
were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was dissolved in 90mL
toluene and 45mL dioxane and treated with 1.12g(12.7mmol) of N, N'-dimethylurea
and 35mL aqueous formaldehyde, followed by warming at reflux for 2.5h. The
35   mixture was cooled and concentrated in vacuo. The residue was chromatographed
over 200g of 230-400 mesh silica gel, eluting with 1-2%(v/v) methanol in chloroform.

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These procedures afforded 3.65g(86%) of the d sired product as an oily yellow solid. MS (EI) *m/z* 351 (M+), 223, 222, 221, 208, 207, 182, 169, 154, 130, 113.

Step 4:   3-Fluoro-1-(phenylmethoxycarbonyl)amino-[*cis*-3-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazin-5-yl)-4-methylpyrrolidinyl]benzene

A solution of 1.82g(5.17mmol) of in 200mL THF was treated with 750mg of 10% palladium on carbon, followed by hydrogenation under 45psi of hydrogen pressure for 3h. The mixture was cooled to -20°C followed by addition of 30mL saturated NaHCO$_3$ solution. The mixture was then treated with 1.10g(0.92mL, 6.46mmol) of benzyl chloroformate, followed by warming to ambient temperature for 18h. The mixture was filtered through celite, washing the filter cake with methanol and dichloromethane. The filtrate was concentrated in vacuo and the residue was dissolved in dichloromethane and extracted with water (3 x 30mL). Drying (Na$_2$SO$_4$) and concentration in vacuo afforded a purple foam which was chromatographed over 125g of 230-300 mesh silica gel, eluting with 1-5% methanol in dichloromethane. These procedures afforded 1.74g(74%) of the title compound as a rigid foam. ^{1}H NMR (CDCl$_3$) δ 7.34, 6.92, 6.53, 5.18, 4.19, 4.13, 3.69, 3.58, 3.52, 3.41, 3.15, 2.86, 2.37, 1.05.

Step 5:   (R)-(3-(3-Fluoro-4-(*cis*-3-(1,3-dimethylhexahydro-2-oxo-1, 3, 5-triazin-5-yl)-4-methylpyrrolidinyl)phenyl)-2-oxo-5-oxazolidinyl)methanol

A solution of 860mg(1.89mmol) of the previous compound in 25mL THF at -78°C was treated with 1.3mL(2.08mmol) of n-butyllithium in hexane, followed by warming to -50°C. After stirring at -50°C for 20 minutes, 286mg(0.28mL, 1.98mmol) of (R)-(-)-glycidiyl butyrate was added. The mixture was warmed to 0°C for 30 minutes and then to ambient temperature for 18h. The mixture was treated with saturated NH$_4$Cl solution and was diluted with ethyl acetate and then extracted with water (3 x). The aqueous phase was extracted with ethyl acetate and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo to afford a brown oil. This material was chromatographed over 40g of 230-400 mesh silica gel, eluting with methanol in dichloromethane. These procedures afforded 512mg(64%) of the title compound as a white rigid foam. ^{1}H NMR (CDCl$_3$) δ 7.35, 7.03, 6.60, 4.72, 4.22, 4.14, 3.94, 3.75, 3.70 , 3.60, 3.54, 3.43, 3.18, 2.87, 2.39, 1.05.

Step 6:   (R)-(3-(3-Fluoro-4-(*cis*-3-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazin-5-yl)-4-methylpyrrolidinyl)phenyl)-2-oxo-5-oxazolidinyl)methanesulfonyloxymethane

A solution of 1g(2.37mmol) of the previous compound and 480mg(0.66mL,

4.74mmol) of triethylamine in 15mL dichloromethane at 0°C was treated with 407mg(0.28mL, 3.56mmol) of methanesulfonyl chloride. The s lution was stirred at 0°C for 1.5h, followed by warming, dilution with dichloromethane and extraction with water (3 x). The organic layer was dried (Na₂SO₄) and concentrated in vacuo to afford the title compound. ¹H NMR (CDCl₃) δ 7.45, 7.02, 6.92, 4.92, 4.50 (, 1 H), 4.43, 4.23, 4.17, 3.91, 3.83, 3.65, 3.50, 3.29, 3.11, 2.89, 2.48, 1.12.

Step 7: (S)-(N)-((3-Fluoro-4-(cis-3-(1,3-dimethylhexahydro-2-oxo-1,3,5-triazin-5-yl)-4-methylpyrrolidinyl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide

A solution of the previous mesylate in 6mL THF and 6mL isopropyl alcohol was treated with 6mL of concentrated ammonium hydroxide. The mixture was warmed at 100°C in a sealed tube for 48h. The mixture was cooled and diluted with ethyl acetate and water. The mixture was extracted with ethyl acetate (2 x). The mixture was treated with saturated NaCl solution and then extracted with chloroform (3 x). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was dissolved in 15mL pyridine and cooled to 0°C. The solution was treated with 0.5mL acetic anhydride, followed by warming to ambient temperature for 20h. The mixture was concentrated in vacuo and the residue was chromatographed over 75g of 230-400 mesh silica gel eluting with methanol in dichloromethane. These procedures afforded 934mg(85%) of the title compound as a white rigid foam. MS (FAB) m/z 463 (M+H), 464, 463, 462,461, 364, 363, 361, 333, 101, 44.

Step 8: (S)-(N)-((3-Fluoro-4-(cis-3-amino-4-methylpyrrolidinyl)phenyl)-2-oxo-5-oxazolidinyl)methyl)acetamide

A solution of 875mg(1.89mmol) of the previous compound in 5mL of 2N HCl solution was stirred at ambient temperature for 20h. The solution was concentrated in vacuo, and the residue was dried by azeotroping with toluene. These procedures afforded 662mg(ca. 100%) of the title compound as an amber rigid foam. MS (FAB) m/z 351 (M+H), 427, 352, 351, 350, 349, 255, 123, 101, 89, 44. HRMS (FAB) calcd for $C_{17}H_{23}FN_4O_3+H_1$ 351.1832, found 351.1840.

Step 9: (S)-N-((3-Fluoro-4-(cis-3-(methoxycarbonylamino)-4-methylpyrrolidinyl)phenyl-2-oxo-5-oxazolidinyl)methyl)acetamide

A solution of 150mg(0.43mmol) of the previous compound in 6mL acetone and 3mL water was treated with 108mg(1.29mmol) of NaHCO₃ and cooled to 0°C. The solution was then treated with 89mg(73μL, 0.95mmol) of methyl chloroformate. The solution was then diluted with ethyl acetate and extracted with water (3 x). Drying (Na₂SO₄) and concentration in vacuo afforded a white solid, which was subjected to

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radial chromatography on a 2mm chromatotron plate, eluting with m thanol in dichloromethane. These procedures afforded 155mg(53%) of the title compound as a white solid. MS (EI) m/z 408 (M+), 409, 408, 364, 334, 333, 318, 289, 276, 215, 56.

5   EXAMPLE 15: (S)-N-[[3-Fluoro-4-(cis-3-(hydroxyacetylamino)-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

Step 1:   (S)-N-[[3-Fluoro-4-(cis-3-(phenylmethoxyacetylamino)-4-methylpyrrolidinyl)phenyl]-2-oxo-5-xazolidinyl]methyl]acetamide

A solution of 300mg(0.90mml) of the amine (Example 14, Step 8) in 14mL

10   acetone and 7mL water was treated with 302mg(3.60mmol) of NaHCO$_3$ and cooled to 0°C. The solution was then treated with 414mg(0.35mL, 2.25mmol) of benzyloxyacetyl chloride, followed by warming to ambient temperature for 72h. The mixture was diluted with ethyl acetate and water and the organic layer was extracted with water (3 x). The organic layer was dried (Na$_2$SO$_4$) and concentrated

15   in vacuo to afford a brown oil. This material was chromatographed over 30g of 230-400 mesh silica gel, eluting with methanol in dichloromethane. These procedures afforded 132mg(30%) of the title compound as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.57, 7.36, 7.03, 5.98, 4.77, 4.67, 4.63, 4.04, 3.74, 3.70, 3.63, 3.55, 3.45, 3.38, 2.71, 2.03, 1.07.

20   **Step 2:**   (S)-N-[[3-Fluoro-4-(cis-3-(hydroxyacetylamino)-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

A solution of 107mg(0.21mmol) of the previous compound in 25mL methanol was treated with 100mg of 10% palladium on carbon followed by hydrogenation at one atmosphere for 72h. The mixture was filtered through celite, and the filtrate

25   was concentrated in vacuo. The residue was subjected to radial chromatography on a 2mm chromatotron plate, eluting with methanol in dichloromethane. These procedures afforded 24mg(8%) of the title compound as a light beige solid. MS (EI) m/z 408 (M+), 408, 334, 333, 318, 289, 215, 70, 57, 56, 55.

30   EXAMPLE 16: (S)-N-[[3-Fluoro-4-(cis-3-(methanesulfonylamino)-4-methylpyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

A slurry of 200mg(0.57mmol) of the amine (Example 14, Step 8) in 10mL dichloromethane was treated with 144mg(0.20mL, 1.43mmol) of triethylamine, followed by cooling of the resulting solution to 0°C. The mixture was treated with

35   83mg(56μL, 0.73mmol) of methanesulfonyl chloride, followed by warming at ambient temperature for 18h. The mixture was diluted with 50mL ethyl acetate, followed by
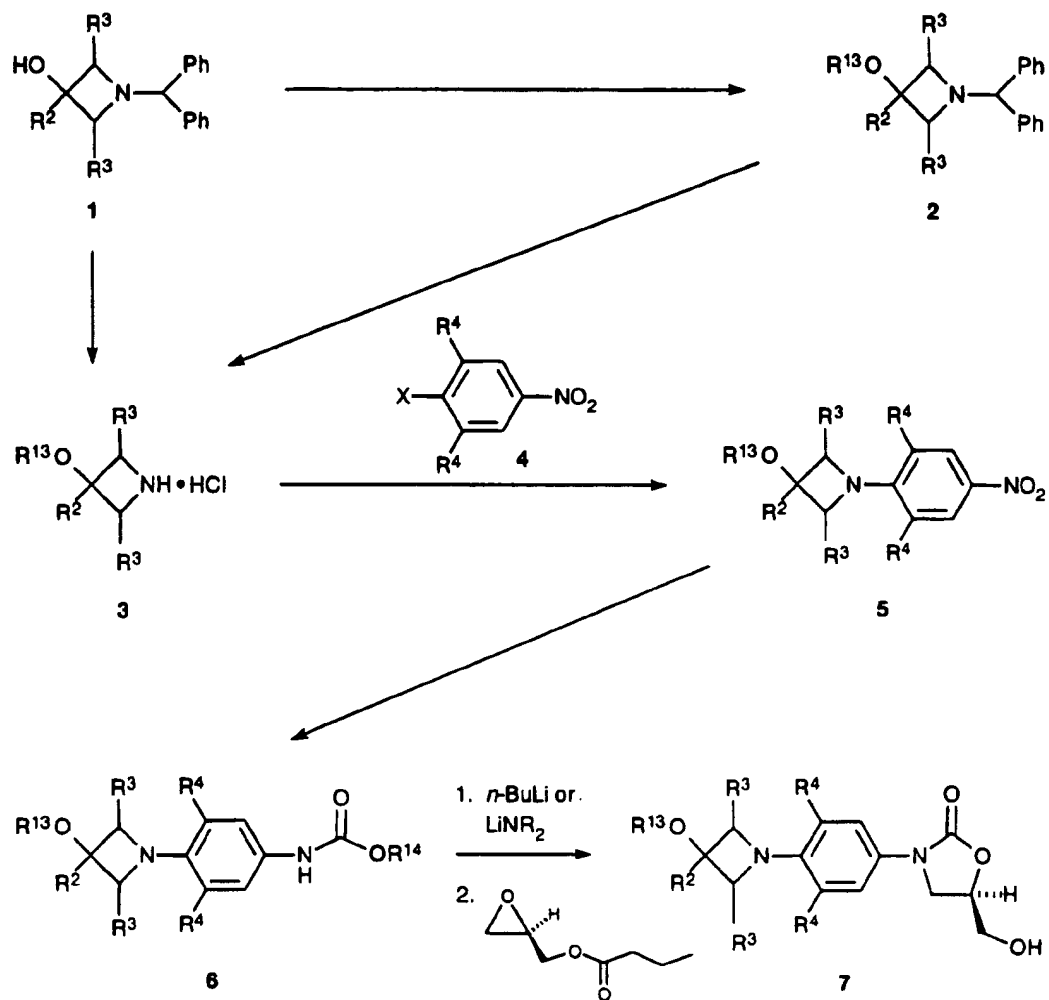
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extraction with water (3 x 30mL). The organic layer was dried (Na$_2$SO$_4$) and
c ncentrated in vacuo to afford an off-white solid, which was subjected to radial
chromatography on a 2mm chromatotron plate, eluting with methanol in
dichloromethane. These procedures afforded 11mg(45%) of the title compound as a
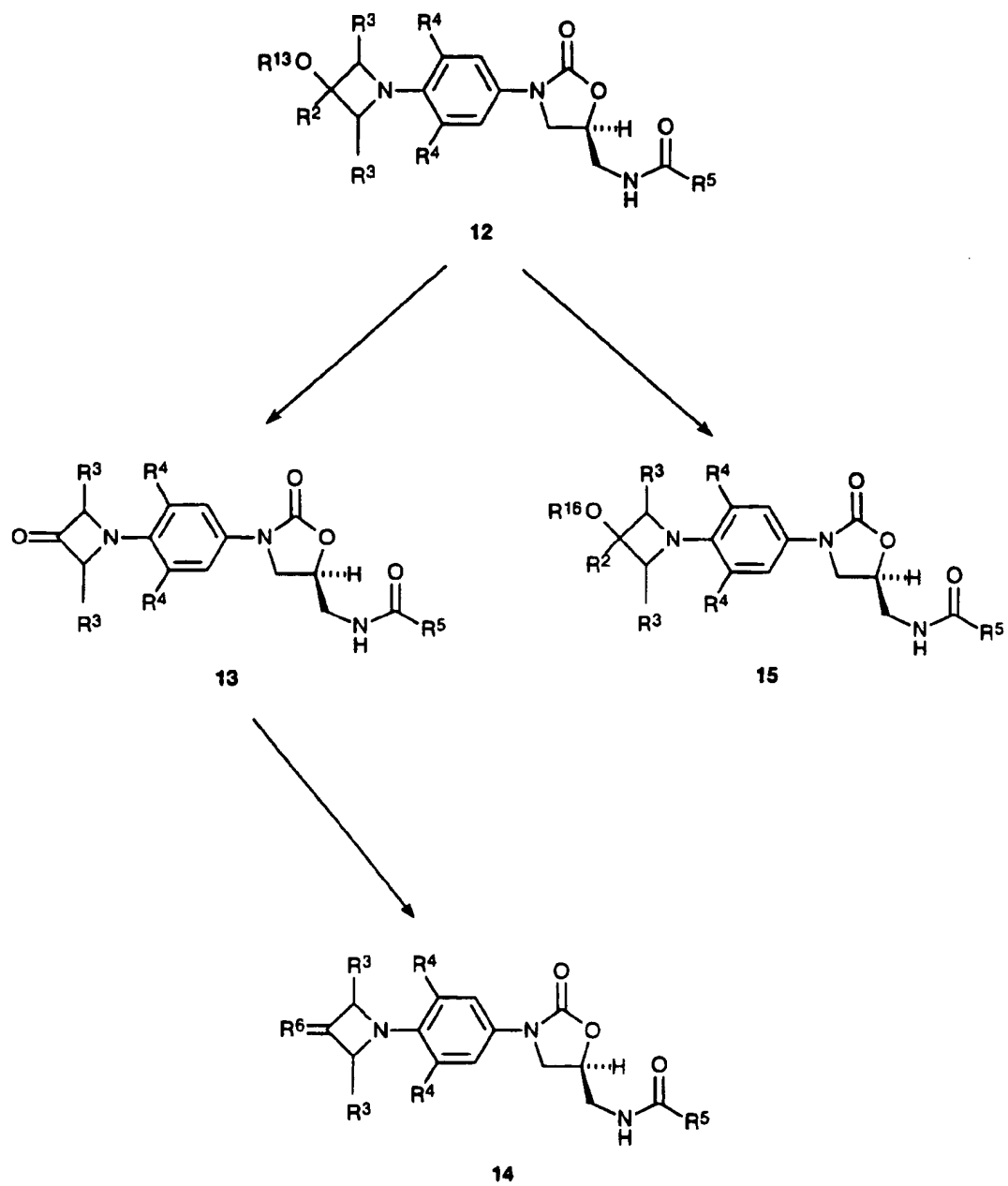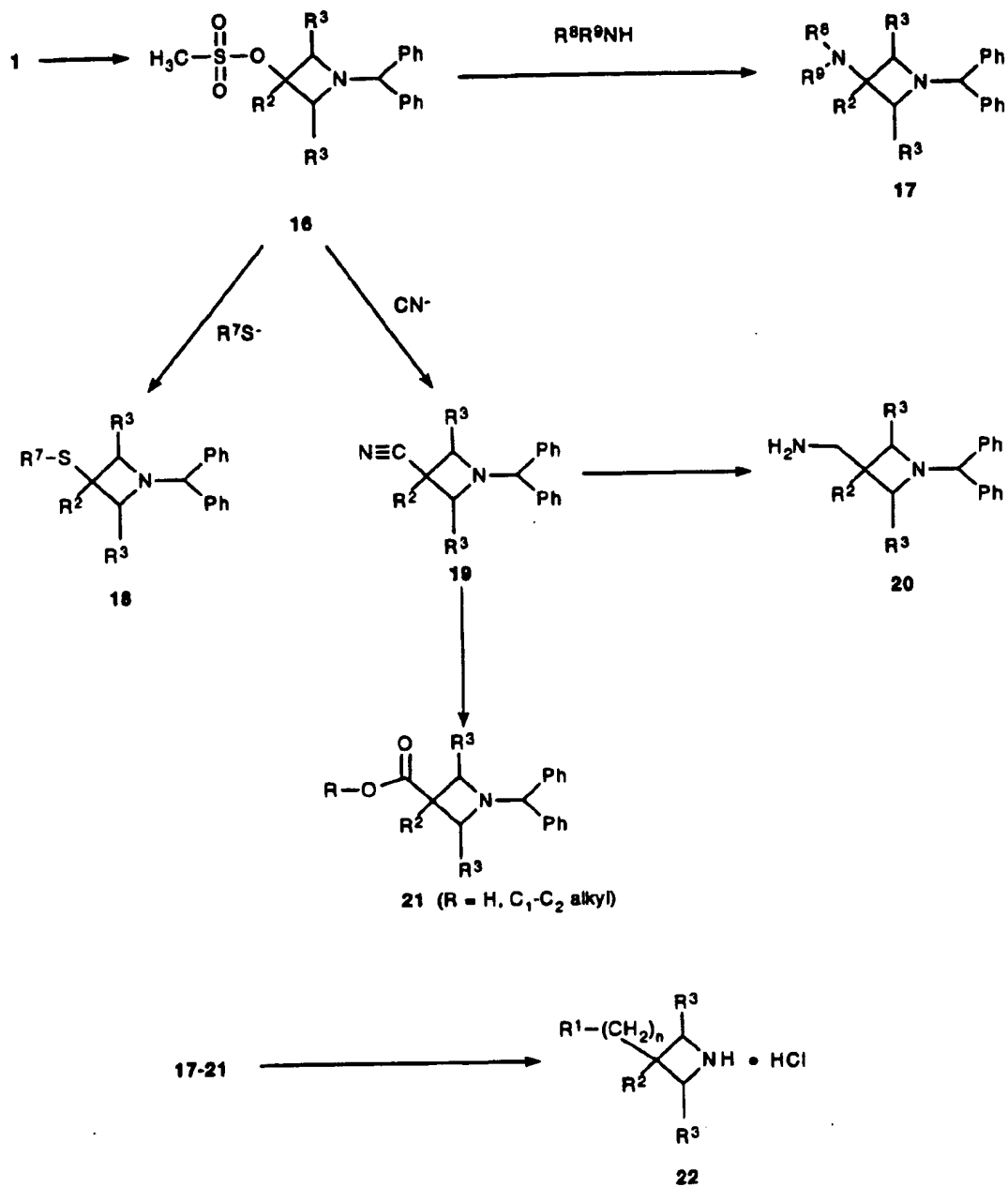5   white solid. MS (EI) m/z 428 (M+), 429, 428, 384, 300, 280, 238, 236, 177, 70, 56.
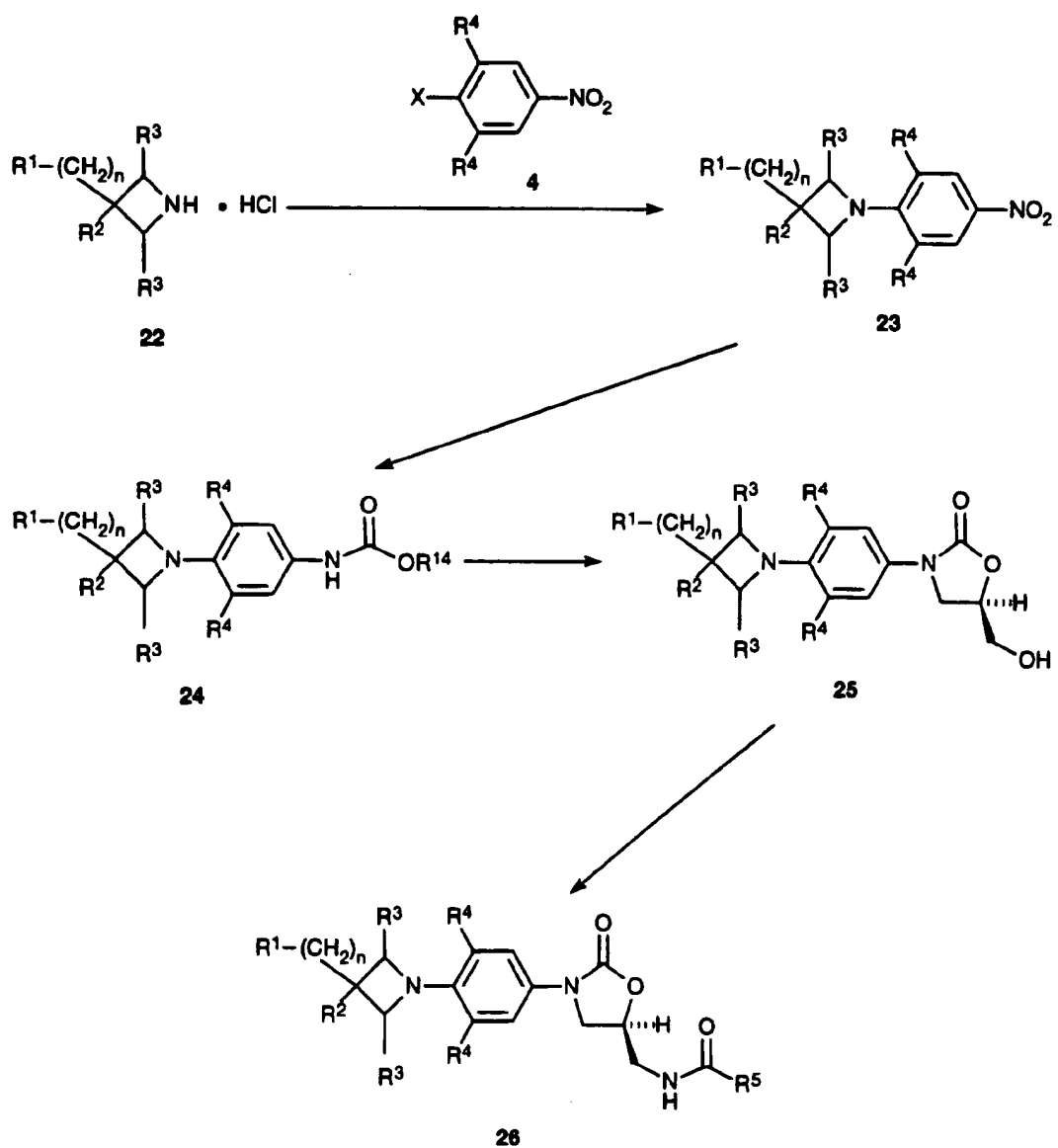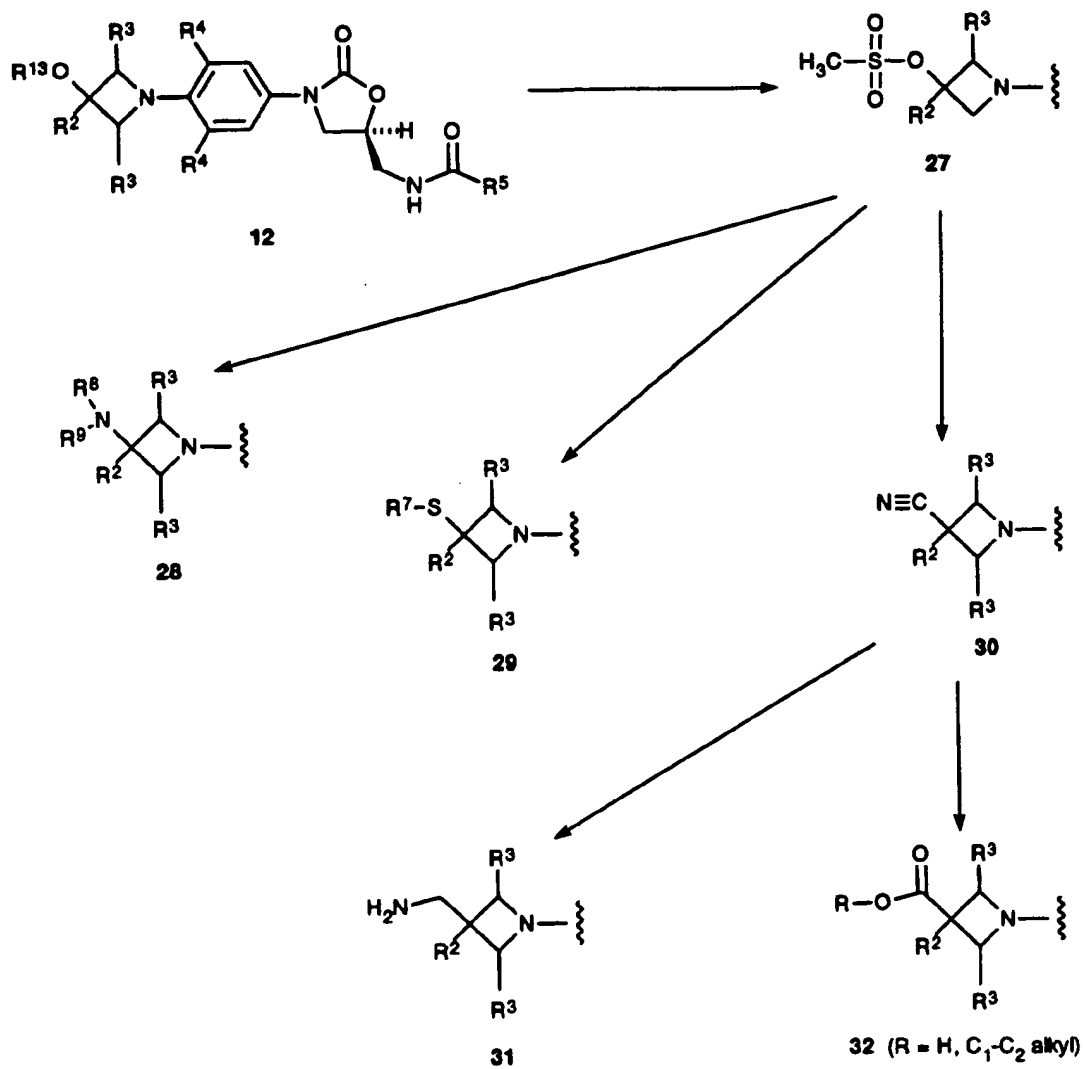
Chart I

Chart II

Chart III

12

13

15

14

Chart IV

21 (R = H, C_1-C_2 alkyl)

22

Chart V

Chart VI

Chart VII

33

1. Base

2.

4

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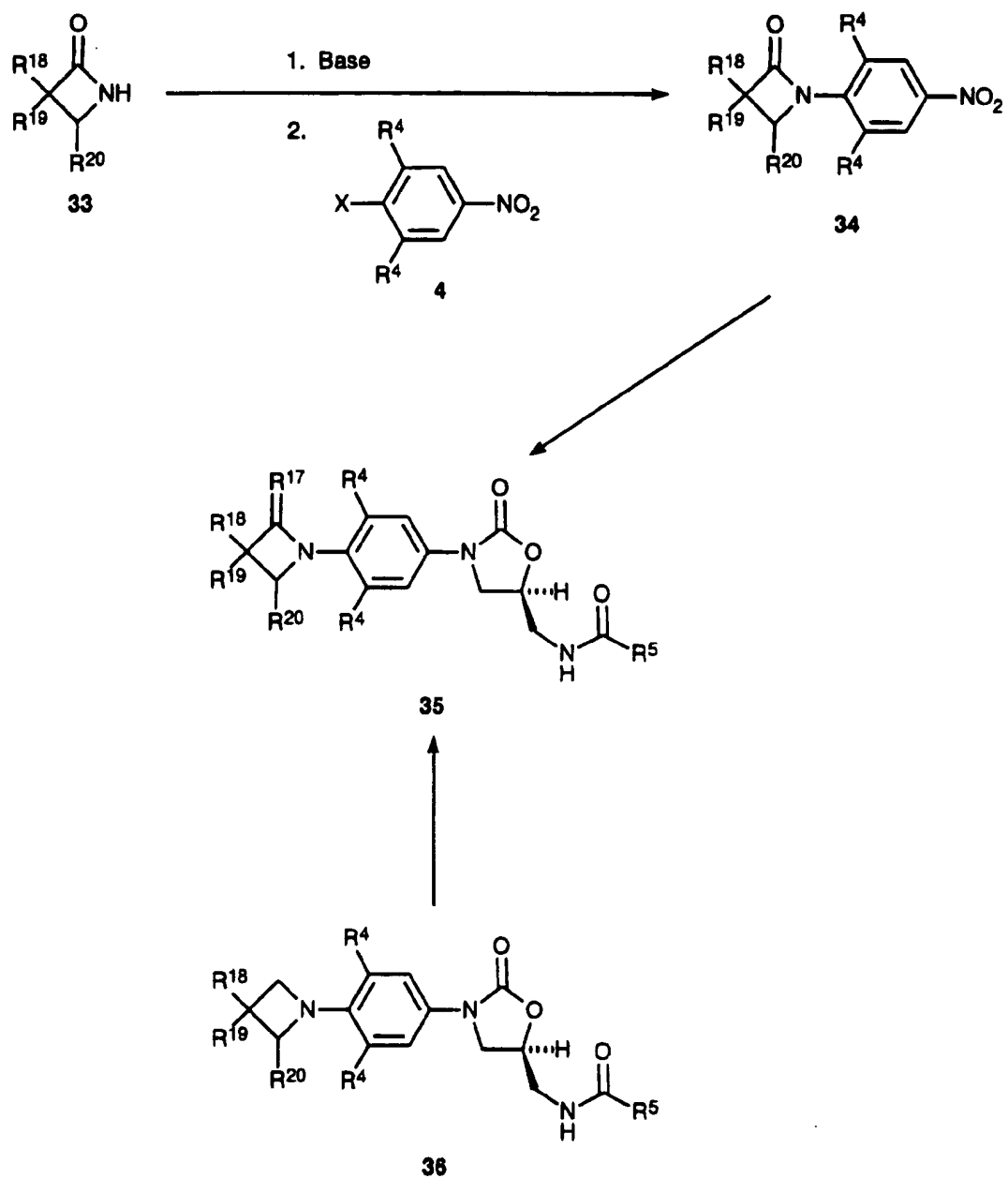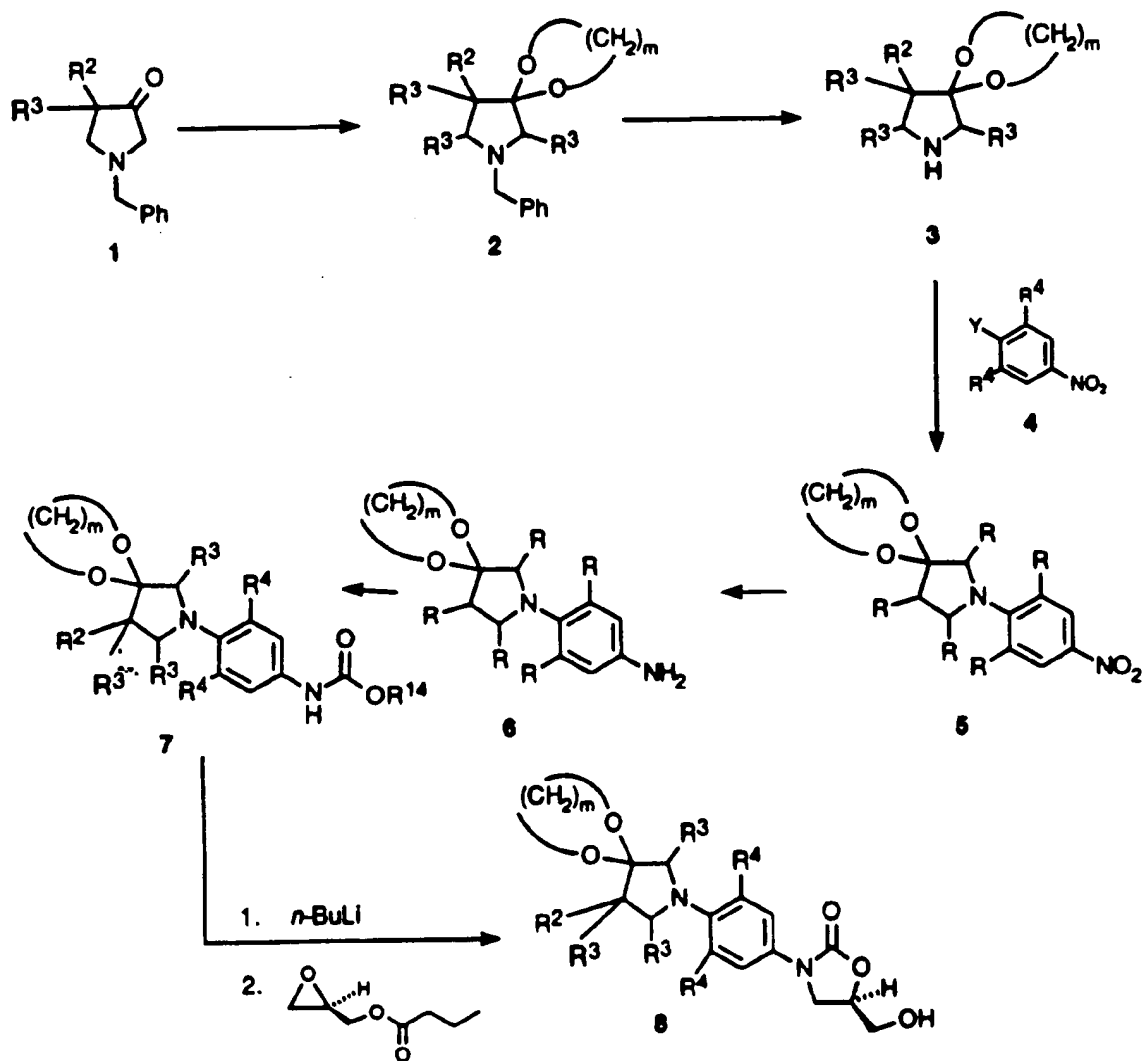
Chart XI

Chart XII

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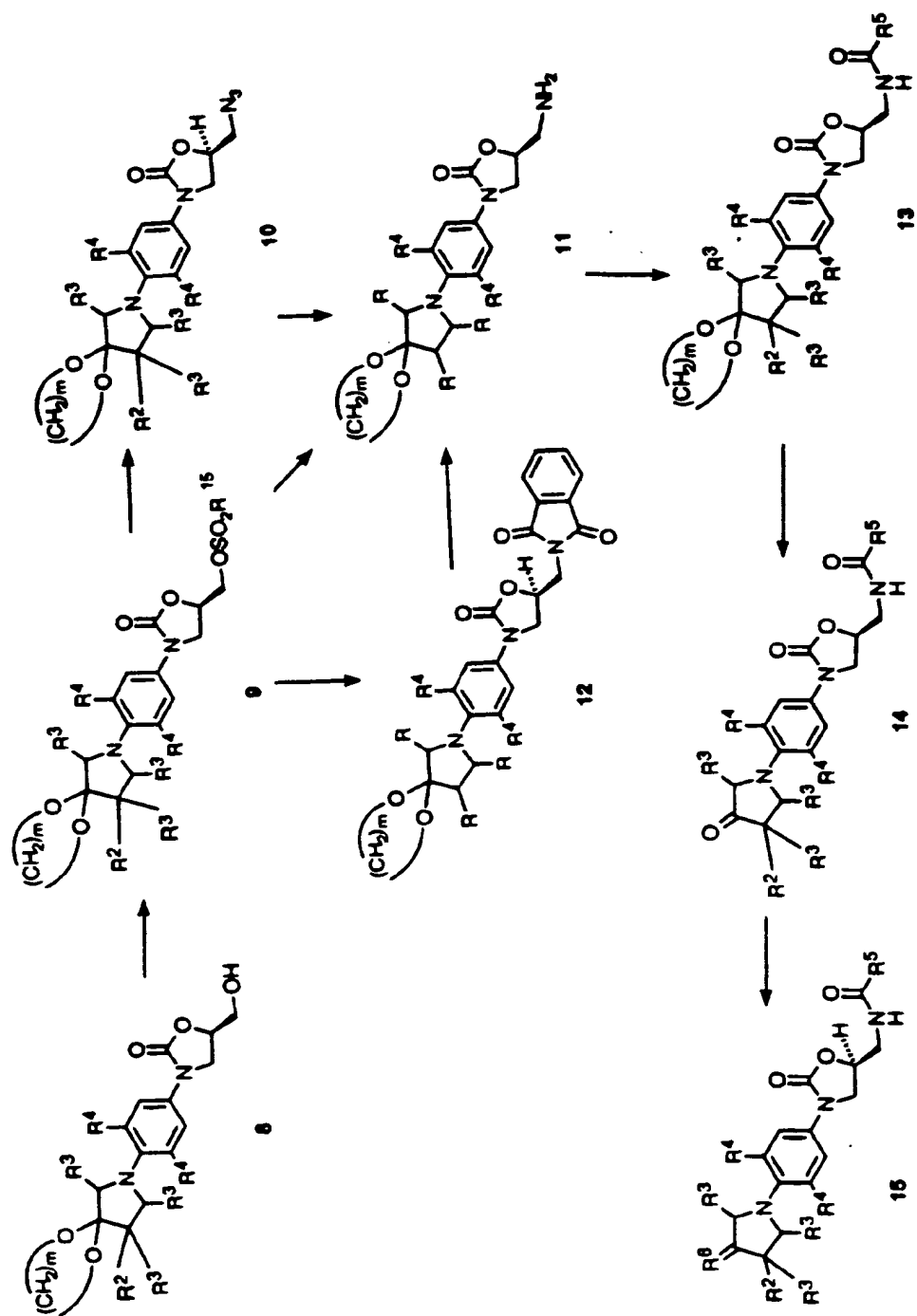
CHART XIII
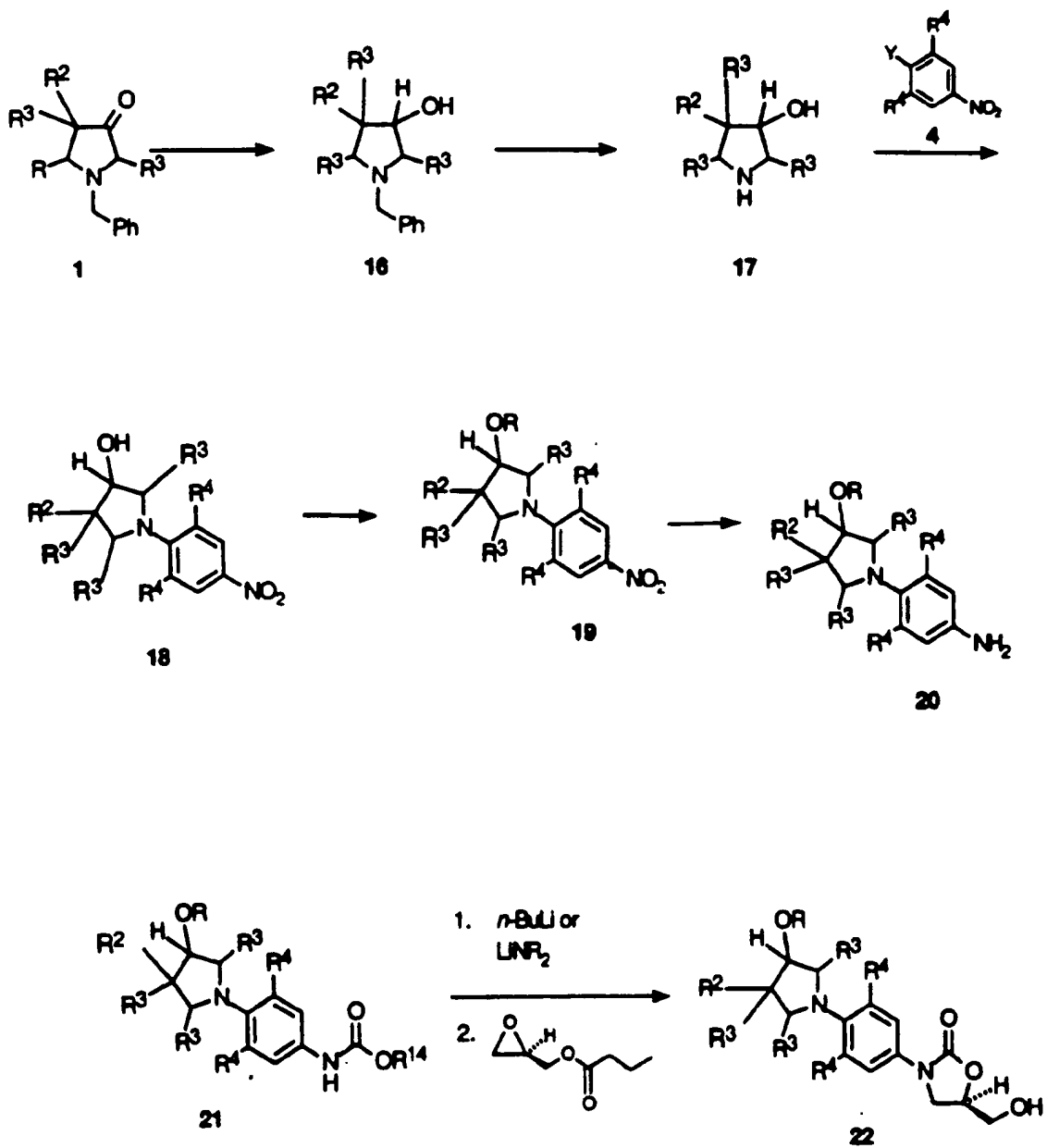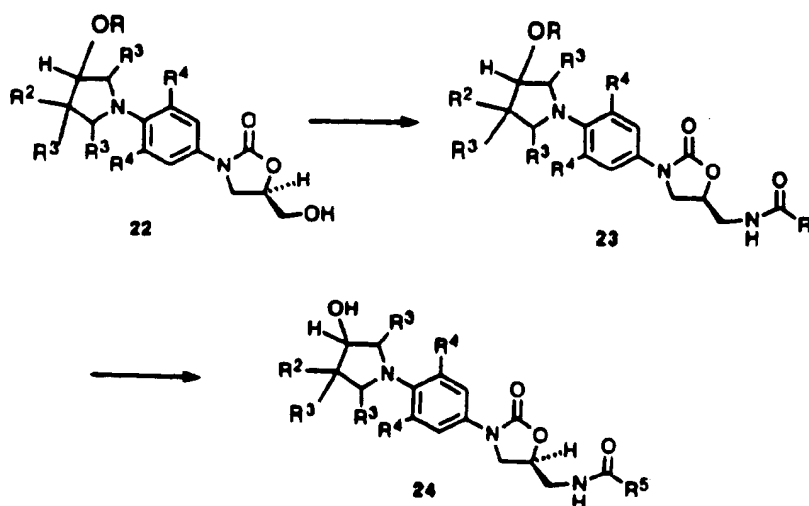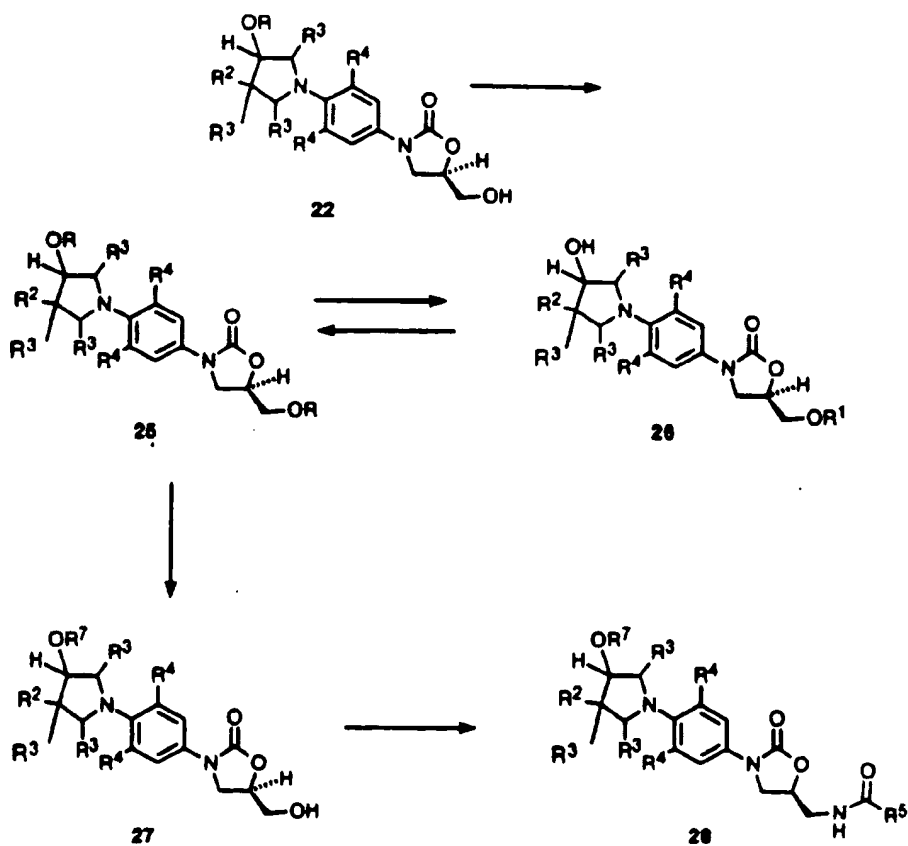
CHART XIV

CHART XV

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CHART XVI

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CHART XVII

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CHART XVIII

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1. *n*-BuLi or LiNR₂

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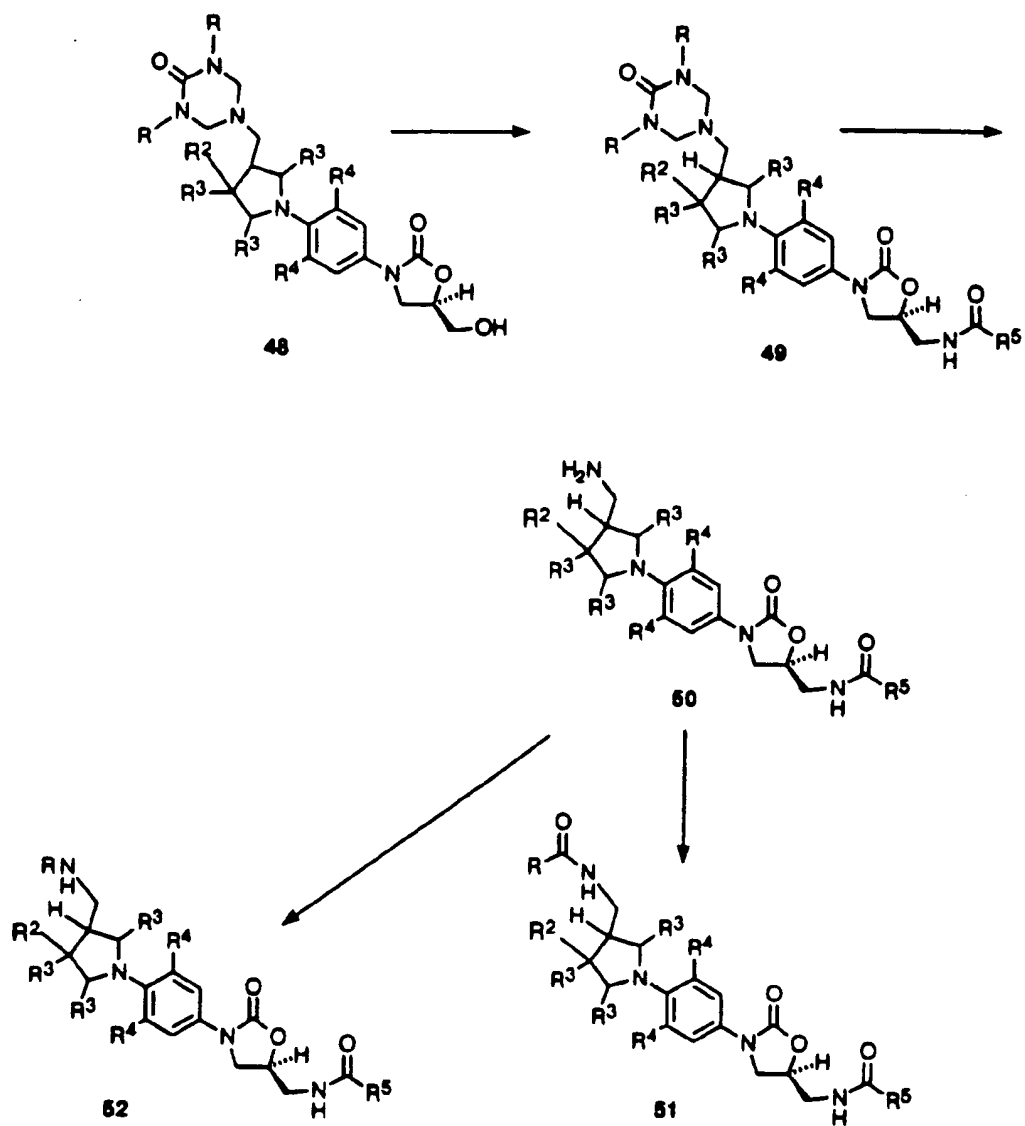## CHART XIX
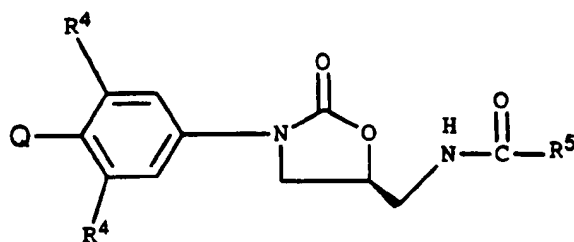

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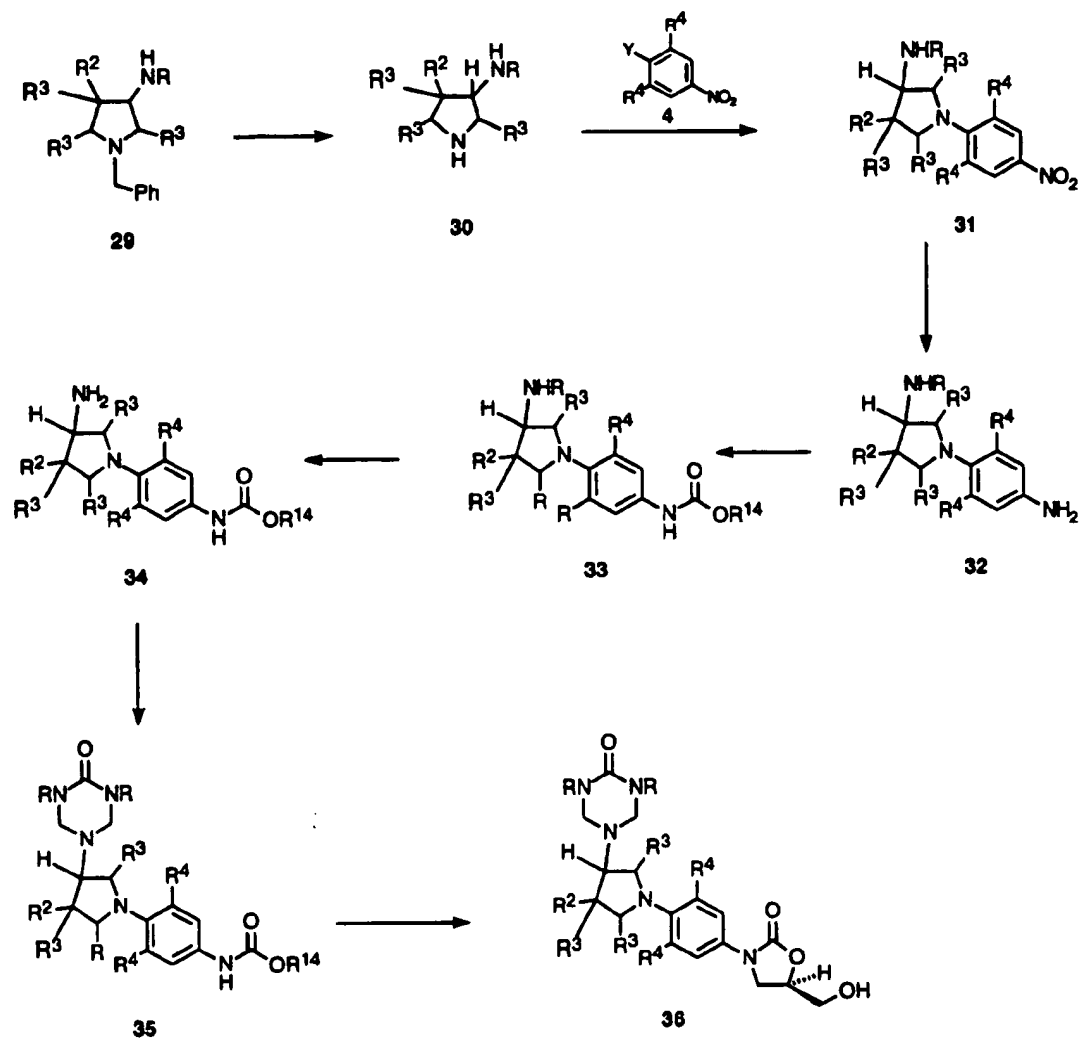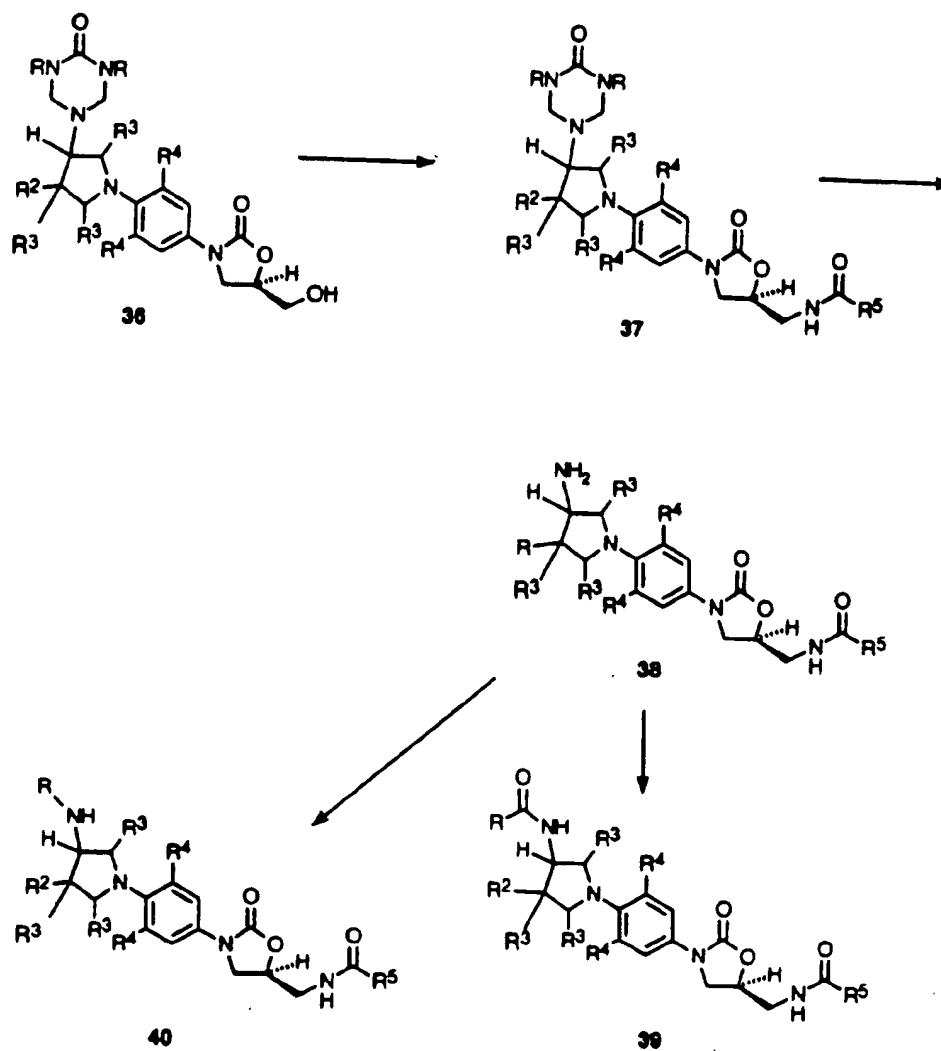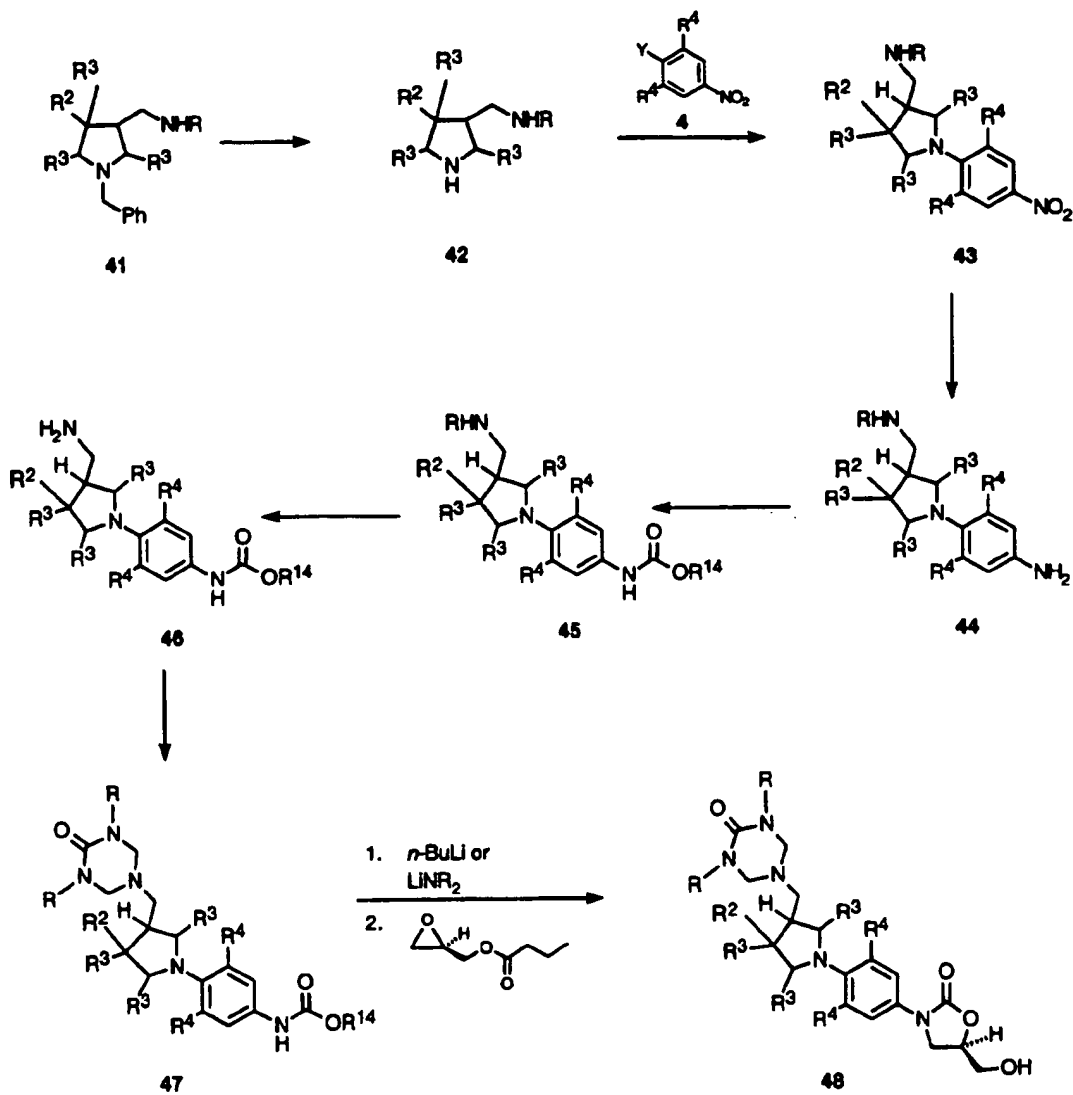
WHAT IS CLAIMED:

1.   A compound of structural Formula I:

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or pharmaceutically acceptable salts thereof wherein:

Q is selected from the structures i, ii, iii, iv and v:

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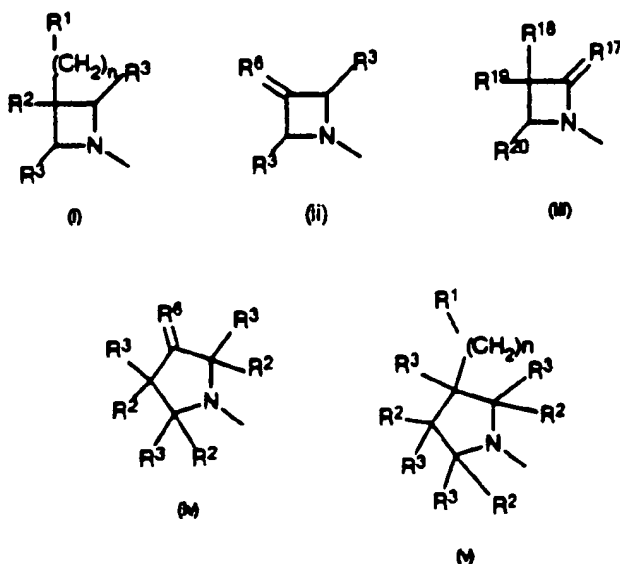
R^1 is   (a)   H or F,

(b) OR^7,

(c) SR^7,

30   (d) NR^8R^9,

(e)   CN,

(f) C_1-C_4 alkoxycarbonyl,

(g)   carboxamide,

(h) C_1-C_4 acyl optionally substituted with one or more of the following:

35   fluorine, hydroxy, C_1-C_4 alkoxy, C_1-C_4 acyloxy,

(i) $NHO(C_1$-C_6 alkyl), $NHOCH_2Ph$,

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    (j) NSO_2R where R is C_{1-6}alkyl optionally substituted with one or more F, Cl, C_{1-6} alkoxy or phenyl;

each R^2 is independently selected from

    (a)   H or F,

5   (b)   OH,

    (c)   OR where R is C_1-C_6 alkyl,

    (d) C_1-C_4 alkyl,

    (e)   Ph;

each R^3 is independently selected from

10   (a)   H,

    (b) C_1-C_3 alkyl which can be optionally substituted with F, Cl, hydroxy, C_1-C_3 alkoxycarbonyl, C_1-C_3 acyloxy, C_1-C_3 alkyoxy or $N(C_1$-C_4 alkyl$)_2$,

    (c)   phenyl,

    (d)   pyridyl;

15 R^4 is independently H, OCH_3, F or Cl;

    R^5 is (a)   hydrogen,

        (b) C_1-C_8 alkyl optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy,

        (c) C_3-C_6 cycloalkyl,

20   (d)   amino,

        (e) C_1-C_8 alkylamino,

        (f) C_1-C_8 dialkylamino,

        (g) C_1-C_8 alkoxy;

    R^6 is (a)   O,

25   (b)   S,

        (c) NR^{10},

        (d) $CR^{11}R^{12}$,

        (e) $(OR)_2$, where R = C_1-C_6 alkyl,

        (f) $O(CH_2)_mO$,

30   (g) $(SR)_2$, where R = C_1-C_6 alkyl,

        (h) $S(CH_2)_mS$

        (i)   to fill the valence OH and H, H and H, H and F or F and F;

    R^7 is (a)   H,

        (b) C_1-C_8 alkyl optionally substituted with one or more of the following:

35   F, Cl, -CN, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy, C_1-C_8 alkoxycarbonyl, phenyl,

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(c) C_1-C_8 acyl optionally substituted with n or m re of the following: hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy,

(d) C_1-C_8 alkoxycarbonyl,

(e) carboxamide, optionally substituted with a C_1-C_4 alkyl or phenyl on the carboxamide nitrogen,

(f) phenyl, optionally substituted with one or more of the following: halogen, CN, C_1-C_3 alkoxy, C_1-C_3 alkoxycarbonyl, C_1-C_4 alkyl optionally substituted with one or more of F or C_1-C_3 alkoxy;

R^8 and R^9 are independently selected from:

(a) H

(b) C_1-C_8 alkyl optionally substituted with one or more of the following: F, Cl, -CN, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy, C_1-C_8 alkoxycarbonyl, phenyl,

(c) C_1-C_8 acyl optionally substituted with one or more of the following: hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy, amino, C_1-C_4 acylamino, amino-C_1-C_4 acylamino,

(d) benzoyl optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy, amino, C_1-C_4 acylamino, C_1-C_4 alkoxycarbonylamino,

(e) C_1-C_8 alkoxycarbonyl, benzyloxycarbonyl, tertbutoxycarbonyl,

(f) carboxamide, optionally substituted with a C_1-C_4 alkyl or phenyl on the carboxamide nitrogen

(g) trifluoracetyl

(h) $CO(C_1$-C_6 alkyl) ;

R^{10} is (a) H,

(b) OR^7,

(c) NHR^7,

(d) C_1-C_8 alkyl optionally substituted with phenyl;

R^{11} and R^{12} are independently selected from:

(a) H, F,

(b) C_1-C_4 alkyl optionally substituted with halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, phenyl,

(c) C_1-C_8 acyl,

(d) C_1-C_4 alkoxycarbonyl,

(e) CN;

R^{17} is (a) O,

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        (b)   S;

R^{18} and R^{19} are independently selected from:

        (a)   H,

        (b) C_1-C_4 alkyl optionally substituted with halogen, hydroxy, C_1-C_4

5 alkoxy,

        (c)   OH,

        (d) C_1-C_4 alkoxy optionally substituted with hydroxy or C_1-C_4 alkoxy,

        (e) NR^8R^9

        (f)   -OC(O)C_1-C_4 alkyl;

10 R^{20} is (a)   H,

        (b) CH_3;

n is 0 or 1 and m is 2 or 3.

2.   The compound of Claim 1 wherein Q is structure (i).

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3.   The compound of Claim 1 wherein Q is structure (ii).

4.   The compound of Claim 1 wherein Q is structure (iii).

20 5.   The compound of Claim 1 wherein Q is structure (iv).

6.   The compound of Claim 1 wherein Q is structure (v).

7.   The compound of Claim 1 wherein each R^4 is fluorine.

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8.   The compound of Claim 1 wherein one R^4 is fluorine and the other is hydrogen.

9.   The compound of Claim 1 wherein R^5 is hydrogen, methoxy or methyl.

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10.   The compound of Claim 1 wherein R^6 is oxygen, OCH_2CH_2O, HOH or $NOCH_3$.

11.   A use of a compound of structural Formula I of Claim 1 for preparing a

35 medicament useful in treating microbial infections in warm blooded animals, including humans by administering to a patient a pharmaceutically effective amount

of the compound.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6   C07D413/10   A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6   C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 09103 (UPJOHN CO) 13 May 1993 cited in the application see claims ---	1,8-11
A	EP,A,0 316 594 (DU PONT DE NEMOURS) 24 May 1989 cited in the application see claims ---	1,8-11
A	EP,A,0 352 781 (DU PONT DE NEMOURS) 31 January 1990 cited in the application see claims ---	1,8-11
A	EP,A,0 359 418 (UPJOHN CO) 21 March 1990 see claims ---	1,8-11

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[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
30 November 1995	11-12-1995

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (- 31-70) 340-3016	Henry, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 127 902 (DU PONT DE NEMOURS) 12 December 1984 see claims	1,8-11

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9309103	13-05-93	AU-A-	2689892	07-06-93
		CA-A-	2119556	13-05-93
		EP-A-	0610265	17-08-94
		JP-T-	7500603	19-01-95
EP-A-0316594	24-05-89	AU-B-	2404388	27-04-89
		CA-A-	1317594	11-05-93
		DE-D-	3884563	04-11-93
		DE-T-	3884563	17-02-94
		ES-T-	2059467	16-11-94
		JP-A-	1135777	29-05-89
		SU-A-	1801109	07-03-93
		US-A-	4977173	11-12-90
EP-A-0352781	31-01-90	US-A-	4948801	14-08-90
		AU-B-	622465	09-04-92
		AU-B-	3911589	01-02-90
		JP-A-	2124877	14-05-90
		US-A-	5130316	14-07-92
		US-A-	5043443	27-08-91
		US-A-	5254577	19-10-93
EP-A-0359418	21-03-90	AT-T-	112773	15-10-94
		AU-B-	617871	05-12-91
		AU-B-	4195789	02-04-90
		CA-A-	1335103	04-04-95
		DE-D-	68918792	17-11-94
		EP-A-	0434714	03-07-91
		EP-A-	0609905	10-08-94
		WO-A-	9002744	22-03-90
		US-A-	5164510	17-11-92
		US-A-	5182403	26-01-93
		US-A-	5225565	06-07-93
		JP-T-	4500665	06-02-92
EP-A-0127902	12-12-84	AU-B-	583250	27-04-89
		AU-B-	2909984	13-12-84
		CA-A-	1254213	16-05-89
		CA-A-	1275652	30-10-90
		DE-A-	3485162	21-11-91

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0127902		JP-A- 60008277	17-01-85
		SU-A- 1505442	30-08-89
		SU-A- 1426451	23-09-88
		US-A- 4705799	10-11-87